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(54) Title: SUPPRESSORS OF CYTOKINE SIGNALING, RELATED REAGENTS			
(57) Abstract			
<p>Purified genes encoding intracellular regulatory molecules from a human, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding these molecules are provided. Methods of using said reagents and diagnostic kits are also provided.</p>			

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SUPPRESSORS OF CYTOKINE SIGNALING; RELATED REAGENTS

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This filing is a PCT Application claiming priority to provisional U.S. Patent Applications USSN 60/055,804, filed August 15, 1997, and USSN 60/053,153, filed July 18, 1997. Also incorporated by reference are provisional 10 U.S. Patent Applications USSN 60/055,853, filed August 15, 1997, and USSN 60/053,244, filed July 18, 1997.

FIELD OF THE INVENTION

The present invention pertains to compositions 15 related to proteins which function, e.g., in suppressing intracellular signaling pathways, e.g., cytokine signaling. In particular, it provides purified genes, proteins, antibodies, and related reagents useful, e.g., to regulate growth hormone-like or cytokine-regulated 20 intracellular processes, including transcription or genes in various cell types, including immune cells.

BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to the 25 technique of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in 30 the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression 35 of the cDNA and thereby direct synthesis of the encoded product in the host.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent 40 research has provided new insights into the inner

workings of this network. While it remains clear that much of the response does, in fact, revolve around the network-like interactions of lymphocytes, macrophages, granulocytes, and other cells, immunologists now 5 generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play a critical role in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell 10 modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders. Some of these factors are hematopoietic growth factors, e.g., granulocyte colony stimulating 15 factor (G-CSF), and others are regulatory molecules. See, e.g., Thomson (1994; ed.) The Cytokine Handbook (2d ed.) Academic Press, San Diego; Metcalf and Nicola (1995) The Hematopoietic Colony Stimulating Factors Cambridge University Press; and Aggarwal and Guterman (1991) Human Cytokines Blackwell Pub.

Lymphokines apparently mediate cellular activities in a variety of ways. They have been shown to support the proliferation, growth, and differentiation of, e.g., pluripotential hematopoietic stem cells into vast numbers 25 of progenitors comprising diverse cellular lineages making up a complex immune system. Proper and balanced interactions between cellular components are necessary for a healthy developmental or immune response. The different cellular lineages often respond in a different 30 manner when lymphokines are administered in conjunction with other agents.

In the immune system, many of the effects of known cytokines on gene transcription are known to be mediated by cytokine inducible DNA binding proteins. See, e.g., 35 Paul (ed. 1994) Fundamental Immunology, 3rd ed., Raven Press, New York, NY. The mechanisms of signal transduction have been an area of active recent study, and involve protein phosphorylation and dephosphorylation with, e.g., the Janus kinases (JAKs) and Signal

Transducers and Activators of Transcription (Stats). See, e.g., Ihle (1996) Cell 84:331-334; ; Ivashkov (1995) Immunity 3:1-4; and Ihle and Kerr (1995) Trends in Genetics 11:69-74.

5 The lack of knowledge regarding the mechanisms of signaling involved in the regulation of cell cycle or transcriptional elements has hampered the ability of medical science to specifically regulate cell division or cellular responses, including immune responses. The
10 present invention provides compositions which will be important in such regulation.

SUMMARY OF THE INVENTION

The present invention is based in part upon the
15 discovery of intracellular regulatory molecules which can block signal transduction, e.g., through growth factor- or cytokine-receptor superfamily signaling mechanisms. These proteins exhibit a structural feature designated a SOCS box. See Hilton, et al. (1998) Proc. Nat'l Acad. Sci. USA 95:114-119. Moreover, the SOCS3 protein can block the IL-2 induced signaling via the STAT5, establishing function of the SOCS proteins as suppressors of cytokine signaling.

The invention provides a substantially pure or recombinant SOCS14 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 2 or 6; a natural sequence SOCS14 of SEQ ID NO: 2 or 6; a fusion protein comprising SOCS14 sequence; a substantially pure or recombinant SOCS15 (also designated
30 WDS11) protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 4 or 8; a natural sequence SOCS15 (WDS11) of SEQ ID NO: 4 or 8; a fusion protein comprising SOCS15 (WDS11) sequence; a substantially pure or recombinant SOCS17
35 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 10; a natural sequence SOCS17 of SEQ ID NO: 10; a fusion protein comprising SOCS17 sequence; a substantially pure or recombinant SOCS18 protein or peptide exhibiting identity
40 over a length of at least about 12 amino acids to SEQ ID

NO: 12; a natural sequence SOCS18 of SEQ ID NO: 12; a fusion protein comprising SOCS18 sequence; a substantially pure or recombinant SOCS19 protein or peptide exhibiting identity over a length of at least 5 about 12 amino acids to SEQ ID NO: 14; a natural sequence SOCS19 of SEQ ID NO: 14; a fusion protein comprising SOCS19 sequence; or a substantially pure or recombinant WDS12 protein or peptide exhibiting identity over a length of at least about 12 amino acids to SEQ ID NO: 16; 10 a natural sequence WDS12 of SEQ ID NO: 16; or a fusion protein comprising WDS12 sequence. In preferred embodiments, the portion is at least about 25 amino acids. In other embodiments, the: SOCS14 comprises a mature sequence of SEQ ID NO: 2 or 6; SOCS15 (WDS11) 15 comprises a mature sequence of SEQ ID NO: 4 or 8; SOCS17 comprises a mature sequence of SEQ ID NO: 10; SOCS18 comprises a mature sequence of SEQ ID NO: 12; SOCS19 comprises a mature sequence of SEQ ID NO: 14; WDS12 comprises a mature sequence of SEQ ID NO: 16; protein or 20 peptide: is from a warm blooded animal selected from a mammal, including a primate; comprises at least one polypeptide segment of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16; exhibits a plurality of portions exhibiting the identity; is a natural allelic variant of SOCS14, SOCS15 25 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a mammalian SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits identity over a length of at least about 20 30 amino acids to SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits at least two non-overlapping epitopes which are specific for a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits identity over a length of at least about 25 amino acids to a primate 35 SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; is glycosylated; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a 40 natural sequence. Various preferred embodiments include

a composition comprising: a sterile SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein or peptide; the SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein or peptide and a carrier,
5 wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration. The invention further provides a fusion protein, comprising: mature protein comprising sequence of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16; a detection or 10 purification tag, including a FLAG, His6, or Ig sequence; or sequence of another SOCS or WDS protein.

These reagents also make available a kit comprising such a protein or polypeptide, and: a compartment 15 comprising the protein or polypeptide; and/or instructions for use or disposal of reagents in the kit.

Providing an antigen, the invention further provides a binding compound comprising an antigen binding portion from an antibody, which specifically binds to a natural 20 SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein, wherein: the protein is a primate protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide 25 sequence of a mature polypeptide comprising sequence of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16; is raised against a mature SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; is raised to a purified SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; is 30 immunoselected; is a polyclonal antibody; binds to a denatured SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12; exhibits a Kd to antigen of at least 30 μ M; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is 35 detectably labeled, including a radioactive or fluorescent label. Preferred kits include those containing the binding compound, and: a compartment comprising the binding compound; and/or instructions for use or disposal of reagents in the kit. Many of the kits

will be used for making a qualitative or quantitative analysis.

Other preferred compositions will be those comprising: a sterile binding compound, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer, and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

The present invention further provides an isolated or recombinant nucleic acid encoding a protein or peptide or fusion protein described above, wherein: the SOCS or WDS family protein is from a mammal, including a primate; or the nucleic acid: encodes an antigenic peptide sequence of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16; encodes a plurality of antigenic peptide sequences of SEQ ID NO: 2, 6, 4, 8, 10, 12, 14 or 16; exhibits identity to a natural cDNA encoding the segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding the SOCS or WDS family protein; or is a PCR primer, PCR product, or mutagenesis primer. In certain embodiments, the invention provides a cell or tissue comprising such a recombinant nucleic acid. Preferred cells include: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Other kit embodiments include a kit comprising the described nucleic acid, and: a compartment comprising the nucleic acid; a compartment further comprising a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein or polypeptide; and/or instructions for use or disposal of reagents in the kit. In many versions, the kit is capable of making a qualitative or quantitative analysis.

Other nucleic acid embodiments include those which: hybridize under wash conditions of 50° C and less than 40 500 mM salt to SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, or 15;

exhibits identity over a stretch of at least about 30 nucleotides to a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12. In other embodiments: the wash conditions are at 55° C and/or 300 mM salt; 60° C and/or 5 150 mM salt; the identity is over a stretch is at least 55 or 75 nucleotides.

In other embodiments, the invention provides a method of modulating physiology or development of a cell or tissue culture cells comprising introducing into such 10 cell an agonist or antagonist of a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 I. General

It is to be understood that this invention is not limited to the particular compositions, methods, and techniques described herein, as such compositions, methods, and techniques may, of course, vary. It is also 20 to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which is only limited by the appended claims.

As used herein, including the appended claims, 25 singular forms of words such as "a," "an," and "the" include their corresponding plural referents unless the context clearly dictates otherwise. Thus, e.g., reference to "a polynucleotide" includes one or more different polynucleotides, reference to "a composition" 30 includes one or more of such compositions, and reference to "a method" include reference to equivalent steps and methods known to a person of ordinary skill in the art, and so forth.

Unless otherwise defined, all technical and 35 scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the 40 present invention, suitable methods and materials are

described below. All publications, patent applications, patents, and other references discussed above are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be 5 construed as an admission that the invention is not entitled to antedate any such disclosure by virtue of its prior invention. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety including all 10 figures, references, and drawings.

The proliferation, differentiation, and physiological responses of many cell lineages are regulated by secreted proteins, e.g., cytokines. These molecules often exert their biological effects through 15 binding to cell surface receptors that are associated with one or more members of the Janus Kinase (Jak) family of cytoplasmic tyrosine kinases. For example, cytokine induced receptor dimerization leads to the activation of JAKs, rapid tyrosine phosphorylation of cytoplasmic 20 domains, and subsequent recruitment of various signaling proteins to the receptor complex, including members of the STAT family of transcription factors. The JAK and STAT proteins are enzymes which act to transduce a signal from the cell surface to the nucleus, thereby serving as 25 the pathway to signal the cell to respond physiologically to an external signal. These pathways have been shown to involve certain protein phosphorylation or dephosphorylation steps, thereby leading to response or lack of response by the cell. See, e.g., Ihle (1996) 30 Cell 84:331-334; Ivashkiv (1995) Immunity 3:1-4; Ihle, et al. (1995) Ann. Rev. Immunol. 13:369-398; Ihle and Kerr (1995) Trends in Genetics 11:69-74; and Darnell, et al. (1994) Science 264:1415-1421.

A number of novel genes have been identified from 35 mouse or humans which appear to inhibit STAT function. See, e.g., Yoshimura, et al. (1995) EMBO J. 14:2816-2826; Matsumoto, et al. (1997) Blood 89:3148-3154; Starr, et al. (1997) Nature 387:917-921; Endo, et al. (1997) Nature 387:921-924; and Naka, et al. Nature 387:924-929. The

present invention provides additional genes with sequence related to those, designated Suppressors Of Cytokine Signaling or WDS: SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12.

5 A primate, e.g., human, SOCS14 cDNA fragment and corresponding open reading frame are provided in (SEQ ID NO: 1 and 2). The translation exhibits significant matching and similarity to other identified SOCS family members. The internal stop codon indicates some errors in the sequence at 10 or near those positions. Additional refined sequence of primate, e.g., human, SOCS14 is provided in SEQ ID NO: 5 and 6.

15 A rodent, e.g., mouse, SOCS15 cDNA fragment and corresponding open reading frame are provided in SEQ ID NO: 3 and 4. The translation exhibits significant matching and similarity to other identified SOCS family members. The internal stop codon indicates some errors in the sequence at or near those positions.

20 A rodent, e.g., murine SOCS17 cDNA and corresponding open reading frame are provided in SEQ ID NO: 9 and 10. Nucleotide may be A, C, T, or G at positions: 1680, 1691, 1696, 1704, 1707, 1728, 1740, 1743, 1746, 1755, 1760, 1770, 1773, 1802, 1816, 1817, 1823, 1826, 1827, 1846, 1851, 1857, 1861, 1880, 1885, 1909, 1917, 1920, 1929, 25 1946, 1953, 1967, 1968, 1980, 1991, 1995, 2001, 2004, 2021, 2033, 2034, 2035, 2036, 2037, 2039, 2040, 2042, 2048, 2051, 2054, 2061, 2075, 2081, 2083, 2084, 2085, 2088, 2105, 2121, 2124, 2132, 2137, 2147, 2149, 2151, 2152, 2160, 2165, 2177, 2179 and 2196; nucleotide may be 30 A or C at position 494; nucleotide may be C or T at positions: 498, 501, 1455, 1524, 1527, 1621, 1829, and 2072; nucleotide may be G or C at positions: 499, 1618, and 1664; nucleotide may be G or T at position 1673; and nucleotide may be A, C, or G at positions: 1819, 1840, 35 and 2089 (see SEQ ID NO: 26).

40 A primate, e.g., human, SOCS18 nucleotide and corresponding amino acid sequence are provided in SEQ ID NO: 11 and 12. Nucleotide may be A or C at positions: 740, 797, 2139, and 2184; nucleotide may be G or T at positions: 761, 1313, 1508, and 2226; nucleotide may be C

or T at positions 746, 1460, 1499, 2009, 2010, 2199, and 2225; nucleotide may be A or G at positions 788, 863, 1550, 2178, 2188, 2197, and 2211; nucleotide may be G or C at positions: 1163, and 1544; nucleotide may be A or T 5 at positions 2058, and 2128; and nucleotide may be A, C, T, or G at position 2251 (see SEQ ID NO: 27).

A primate, e.g., human, SOCS19 nucleotide and corresponding amino acid sequence are provided in SEQ ID NO: 13 and 14. Nucleotide may be A, C, T, or G at 10 positions: 2078, and 2116; and nucleotide may be G or C at position 2063 (see SEQ ID NO: 28).

Finally, a primate, e.g., human, WDS12 nucleotide and corresponding amino acid sequence is provided in SEQ ID NO: 15 and 16. Nucleotide may be A, C, T, or G at 15 positions: 108, and 109; nucleotide may be A or G at positions: 236, 238, and 1258; nucleotide may be G or T at position 233; nucleotide may be G or C at position 234; nucleotide may be C or T at position 237; and nucleotide may be A or T at position 239 (see SEQ ID NO: 29).

SOCS proteins are a family of proteins ranging from approximately 30-60 Kd which inhibit JAK kinase activity. The amino portion of SOCS proteins contain an SH2 binding motif and the carboxy portion of the molecule contains a 25 SOCS box motif which may play a role in dimerization of SOCS proteins. The WDS are closely related in sequence.

SOCS3 expression is induced by IL-2 and can be detected by approximately 1 hour after IL-2 activation. Subsequently, SOCS expression is decreased relatively 30 rapidly (e.g., approximately 8 hrs after activation). Western blots show that SOCS3 interacts with IL-2 receptor and JAK1 following IL-2 stimulation.

II. Definitions

35 The term "binding composition" refers to molecules that bind with specificity to SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein, e.g., in an antibody-antigen interaction. However, other compounds, e.g., binding proteins, may also specifically associate

with SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 proteins in contrast to other molecules. Typically, the association will be in a natural physiologically relevant protein-protein interaction, 5 either covalent or non-covalent, and may include members of a multiprotein complex, including carrier compounds or dimerization partners. The molecule may be a polymer, or chemical reagent. A functional analog may be a protein with structural modifications, or may be a wholly 10 unrelated molecule, e.g., which has a molecular shape which interacts with the appropriate protein binding determinants. The proteins may serve as agonists or antagonists of the binding partner, see, e.g., Goodman, et al. (eds.) (1990) Goodman & Gilman's: The 15 Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press, Tarrytown, N.Y.

The term "binding agent: SOCS or :WDS protein complex", as used herein, refers to a complex of a binding agent and a SOCS14, SOCS15 (WDS11), SOCS17, 20 SOCS18, SOCS19, or WDS12 protein that is formed by specific binding of the binding agent to the respective SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein. Specific binding of the binding agent means that the binding agent has a specific binding site that 25 recognizes a site on the SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein. For example, antibodies raised to a SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein and recognizing an epitope on the SOCS or WDS protein are capable of forming 30 a binding agent: SOCS or :WDS protein complex by specific binding. Typically, the formation of a binding agent: SOCS or :WDS protein complex allows the measurement of SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein in a mixture of other proteins and biologics. 35 The term "antibody: SOCS or :WDS protein complex" refers to an embodiment in which the binding agent, e.g., is an antibody. The antibody may be monoclonal, polyclonal, or a binding fragment of an antibody, e.g., an Fv, Fab, or F(ab)2 fragment. The antibody will preferably be a 40 polyclonal antibody for cross-reactivity purposes.

"Homologous" nucleic acid sequences, when compared, exhibit significant similarity, or identity. The standards for homology in nucleic acids are either measures for homology generally used in the art by 5 sequence comparison and/or phylogenetic relationship, or based upon hybridization conditions. Hybridization conditions are described in greater detail below.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, cDNA, genomic DNA, or a mixed polymer, which 10 is substantially separated from other biologic components which naturally accompany a native sequence, e.g., proteins and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally 15 occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogs, or analogs biologically synthesized by heterologous systems. Further, the term includes double-stranded or single-stranded embodiments. Where single-stranded, the nucleic 20 acid may be either the "sense" or the "antisense" strand. A substantially pure molecule includes isolated forms of the molecule. An isolated nucleic acid will usually contain homogeneous nucleic acid molecules, but will, in some embodiments, contain nucleic acids with minor 25 sequence heterogeneity. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

As used herein, the terms "SOCS" or "WDS" protein shall encompass, when used in a protein context, a 30 protein having amino acid sequences shown in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16 or a significant fragment of such a protein, preferably a natural embodiment. The term "protein" or "polypeptide" is meant any chain of amino acids, regardless of length or posttranslational 35 modification (e.g., glycosylation or phosphorylation). Further, the term encompasses polypeptides which are pre- or pro-proteins. The invention also embraces a polypeptide which exhibits similar structure to SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein, 40 e.g., which interacts with SOCS or WDS protein specific

binding components. These binding components, e.g., antibodies, typically bind to a SOCS or WDS protein, respectively, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably 5 better than about 10 nM, and more preferably at better than about 3 nM.

The term "polypeptide" or "protein" as used herein includes a significant fragment or segment of a SOCS or WDS protein, and encompasses a stretch of amino acid 10 residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 15 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids, e.g., 35, 40, 45, 50, 60, 70, 80, etc. The invention 20 encompasses proteins comprising a plurality of distinct, e.g., nonoverlapping, segments of the specified length. Typically, the plurality will be at least two, more usually at least three, and preferably 5, 7, or even more. While the length minima are provided, longer 25 lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12. Features of one of the different genes should not be taken to limit those of another of the genes.

A "recombinant" nucleic acid is defined either by 30 its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence, typically selection or production. 35 Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants. Thus, for example, products made by 40 transforming cells with any non-naturally occurring

vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic oligonucleotide process. Such is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a sequence recognition site. Alternatively, it is performed to join together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly 5 available natural forms. Restriction enzyme recognition sites are often the target of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be 10 incorporated by design. A similar concept is intended for a recombinant, e.g., fusion, polypeptide. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode polypeptides similar to fragments of these antigens, and fusions of sequences 15 from various different species variants.

"Solubility" is reflected by sedimentation measured in Svedberg units, which are a measure of the sedimentation velocity of a molecule under particular conditions. The determination of the sedimentation 25 velocity was classically performed in an analytical ultracentrifuge, but is typically now performed in a standard ultracentrifuge. See, Freifelder (1982) Physical Biochemistry (2d ed.) W.H. Freeman & Co., San Francisco, CA; and Cantor and Schimmel (1980) Biophysical 30 Chemistry parts 1-3, W.H. Freeman & Co., San Francisco, CA. As a crude determination, a sample containing a putatively soluble polypeptide is spun in a standard full sized ultracentrifuge at about 50K rpm for about 10 minutes, and soluble molecules will remain in the 35 supernatant. A soluble particle or polypeptide will typically be less than about 30S, more typically less than about 15S, usually less than about 10S, more usually less than about 6S, and, in particular embodiments, preferably less than about 4S, and more preferably less 40 than about 3S. Solubility of a polypeptide or fragment

depends upon the environment and the polypeptide. Many parameters affect polypeptide solubility, including temperature, electrolyte environment, size and molecular characteristics of the polypeptide, and nature of the solvent. Typically, the temperature at which the polypeptide is used ranges from about 4° C to about 65° C. Usually the temperature at use is greater than about 18° C and more usually greater than about 22° C. For diagnostic purposes, the temperature will usually be about room temperature or warmer, but less than the denaturation temperature of components in the assay. For therapeutic purposes, the temperature will usually be body temperature, typically about 37° C for humans, though under certain situations the temperature may be raised or lowered in situ or in vitro.

The size and structure of the polypeptide should generally be in a substantially stable state, and usually not in a denatured state. The polypeptide may be associated with other polypeptides in a quaternary structure, e.g., to confer solubility, or associated with lipids or detergents in a manner which approximates natural lipid bilayer interactions.

The solvent will usually be a biologically compatible buffer, of a type used for preservation of biological activities, and will usually approximate a physiological solvent. Usually the solvent will have a neutral pH, typically between about 5 and 10, and preferably about 7.5. On some occasions, a detergent will be added, typically a mild non-denaturing one, e.g., CHS (cholesteryl hemisuccinate) or CHAPS (3-[3-cholamidopropyl]-dimethylammonio]-1-propane sulfonate), or a low enough concentration as to avoid significant disruption of structural or physiological properties of the protein.

"Substantially pure" in a protein context typically means that the protein is isolated from other contaminating proteins, nucleic acids, and other biologicals derived from the original source organism. Purity, or "isolation" may be assayed by standard methods, and will ordinarily be at least about 50% pure,

more ordinarily at least about 60% pure, generally at least about 70% pure, more generally at least about 80% pure, often at least about 85% pure, more often at least about 90% pure, preferably at least about 95% pure, more 5 preferably at least about 98% pure, and in most preferred embodiments, at least 99% pure. Similar concepts apply, e.g., to antibodies or nucleic acids.

"Substantial similarity" in the nucleic acid sequence comparison context means either that the 10 segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 50% of the nucleotides, generally at least 56%, more generally at least 59%, ordinarily at least 62%, more 15 ordinarily at least 65%, often at least 68%, more often at least 71%, typically at least 74%, more typically at least 77%, usually at least 80%, more usually at least about 85%, preferably at least about 90%, more preferably at least about 95 to 98% or more, and in particular 20 embodiments, as high as about 99% or more of the nucleotides. Alternatively, substantial similarity exists when the segments will hybridize under selective hybridization conditions, to a strand, or its complement, typically using a sequence derived from SEQ ID NO: 1, 3, 25 5, 7, 9, 11, 13, or 15. Typically, selective hybridization will occur when there is at least about 55% similarity over a stretch of at least about 30 nucleotides, preferably at least about 65% over a stretch of at least about 25 nucleotides, more preferably at 30 least about 75%, and most preferably at least about 90% over about 20 nucleotides. See Kanehisa (1984) Nuc. Acids Res. 12:203-213. The length of similarity comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at 35 least about 17 nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 40 100 or more nucleotides, e.g., 150, 200, etc.

For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are input into a computer, 5 subsequent coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence identity for the test sequence(s) relative to the reference sequence, based on the 10 designated program parameters.

Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the homology alignment algorithm of Needleman and Wunsch 15 (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer 20 Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel et al., *supra*).

One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments 25 to show relationship and percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The 30 method used is similar to the method described by Higgins and Sharp (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two 35 most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a simple extension of the pairwise alignment of two 40 individual sequences. The final alignment is achieved by

a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison and by designating the program 5 parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps.

10 Another example of algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described Altschul, et al. (1990) J. Mol. Biol. 215:403-410. Software for performing BLAST analyses is publicly 15 available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some 20 positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul, et al., *supra*). These initial neighborhood word hits act as seeds for initiating searches to find 25 longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the 30 quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the 35 sensitivity and speed of the alignment. The BLAST program uses as defaults a word length (W) of 11, the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) Proc. Nat'l Acad. Sci. USA 89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of 40 both strands.

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) Proc. Nat'l Acad. Sci. USA 90:5873-5878). One measure of similarity provided by the BLAST algorithm is the smallest sum probability ($P(N)$), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below.

Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions.

Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

"Stringent conditions", in referring to homology or substantial similarity in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters, typically those controlled in hybridization reactions. The combination of parameters is more important than the measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370.

A nucleic acid probe which binds to a target nucleic acid under stringent conditions is specific for said target nucleic acid. Hybridization under stringent conditions should give a background of at least 2-fold over background, preferably at least 3-5 or more. Such a probe is typically more than 11 nucleotides in length,

and is sufficiently identical or complementary to a target nucleic acid over the region specified by the sequence of the probe to bind the target under stringent hybridization conditions.

5 SOCS14, SOCS15 (WDS11), SOCS17, SOCS18, SOCS19, or WDS12 protein from other mammalian species can be cloned and isolated by cross-species hybridization of closely related species. See, e.g., below. Similarity may be relatively low between distantly related species, and
10 thus hybridization of relatively closely related species is advisable. Alternatively, preparation of an antibody preparation which exhibits less species specificity may be useful in expression cloning approaches.

15 The phrase "specifically binds to an antibody" or "specifically immunoreactive with", when referring to a protein or peptide, refers to a binding reaction which is determinative of the presence of the protein in the presence of a heterogeneous population of proteins and other biological components. Thus, under designated
20 immunoassay conditions, the specified antibodies bind to a particular protein and do not significantly bind other proteins present in the sample. Specific binding to an antibody under such conditions may require an antibody that is selected for its specificity for a particular
25 protein. For example, antibodies raised to the protein immunogen with the amino acid sequence depicted in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16 can be selected to obtain antibodies specifically immunoreactive with SOCS or WDS proteins and not with other proteins. These
30 antibodies recognize proteins highly similar to the homologous SOCS or WDS protein.

III. Nucleic Acids

35 Primate or rodent SOCS or WDS protein is each exemplary of a larger class of structurally and functionally related proteins. These soluble proteins will serve to transmit signals between different cell types. The preferred embodiments, as disclosed, will be useful in standard procedures to isolate genes from
40 different individuals or other species, e.g., warm

blooded animals, such as birds and mammals. Cross hybridization will allow isolation of related genes encoding proteins from individuals, strains, or species. A number of different approaches are available to 5 successfully isolate a suitable nucleic acid clone based upon the information provided herein. Southern blot hybridization studies can qualitatively determine the presence of homologous genes in human, monkey, rat, mouse, dog, cow, and rabbit genomes under specific 10 hybridization conditions.

Complementary sequences will also be used as probes or primers. Based upon identification of the likely amino terminus, other peptides should be particularly useful, e.g., coupled with anchored vector or poly-A 15 complementary PCR techniques or with complementary DNA of other peptides.

Techniques for nucleic acid manipulation of genes encoding SOCS or WDS proteins, such as subcloning nucleic acid sequences encoding polypeptides into expression 20 vectors, labeling probes, DNA hybridization, and the like are described generally in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2nd ed.) Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY, which is incorporated herein by reference. 25 This manual is hereinafter referred to as "Sambrook, et al."

There are various methods of isolating DNA sequences 30 encoding SOCS or WDS proteins. For example, DNA is isolated from a genomic or cDNA library using labeled oligonucleotide probes having sequences identical or complementary to the sequences disclosed herein. Full-length probes may be used, or oligonucleotide probes may be generated by comparison of the sequences disclosed. Such probes can be used directly in hybridization assays 35 to isolate DNA encoding SOCS or WDS proteins, or probes can be designed for use in amplification techniques such as PCR, for the isolation of DNA encoding SOCS or WDS proteins.

To prepare a cDNA library, mRNA is isolated from 40 cells which expresses a SOCS or WDS protein. cDNA is

prepared from the mRNA and ligated into a recombinant vector. The vector is transfected into a recombinant host for propagation, screening, and cloning. Methods for making and screening cDNA libraries are well known.

5 See Gubler and Hoffman (1983) Gene 25:263-269 and Sambrook, et al.

For a genomic library, the DNA can be extracted from tissue and either mechanically sheared or enzymatically digested to yield fragments of about 12-20 kb. The 10 fragments are then separated by gradient centrifugation and cloned in bacteriophage lambda vectors. These vectors and phage are packaged in vitro, as described in Sambrook, et al. Recombinant phage are analyzed by plaque hybridization as described in Benton and Davis 15 (1977) Science 196:180-182. Colony hybridization is carried out as generally described in e.g., Grunstein, et al. (1975) Proc. Natl. Acad. Sci. USA 72:3961-3965.

DNA encoding a SOCS14 or SOCS15 protein can be identified in either cDNA or genomic libraries by its 20 ability to hybridize with the nucleic acid probes described herein, e.g., in colony or plaque hybridization assays. The corresponding DNA regions are isolated by standard methods familiar to those of skill in the art. See, e.g., Sambrook, et al.

25 Various methods of amplifying target sequences, such as the polymerase chain reaction, can also be used to prepare DNA encoding SOCS or WDS proteins. Polymerase chain reaction (PCR) technology is used to amplify such nucleic acid sequences directly from mRNA, from cDNA, and 30 from genomic libraries or cDNA libraries. The isolated sequences encoding SOCS or WDS proteins may also be used as templates for PCR amplification.

Typically, in PCR techniques, oligonucleotide primers complementary to two 5' regions in the DNA region 35 to be amplified are synthesized. The polymerase chain reaction is then carried out using the two primers. See Innis, et al. (eds.) (1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA. Primers can be selected to amplify the entire regions 40 encoding a full-length SOCS or WDS protein or to amplify

smaller DNA segments as desired. Once such regions are PCR-amplified, they can be sequenced and oligonucleotide probes can be prepared from sequence obtained using standard techniques. These probes can then be used to 5 isolate DNA's encoding SOCS or WDS proteins.

Oligonucleotides for use as probes are usually chemically synthesized according to the solid phase phosphoramidite triester method first described by Beaucage and Carruthers (1983) Tetrahedron Lett.
10 22(20):1859-1862, or using an automated synthesizer, as described in Needham-VanDevanter, et al. (1984) Nucleic Acids Res. 12:6159-6168. Purification of oligonucleotides is performed e.g., by native acrylamide gel electrophoresis or by anion-exchange HPLC as 15 described in Pearson and Regnier (1983) J. Chrom. 255:137-149. The sequence of the synthetic oligonucleotide can be verified using, e.g., the chemical degradation method of Maxam, A.M. and Gilbert, W. in Grossman, L. and Moldave (eds.) (1980) Methods in 20 Enzymology 65:499-560 Academic Press, New York.

Isolated nucleic acids encoding SOCS or WDS proteins were identified. The nucleotide sequences and corresponding open reading frames are provided in SEQ ID NO: 1 through 16.

25 These SOCS or WDS proteins exhibit limited similarity to portions other intracellular proteins. In particular, β -sheet and α -helix residues can be determined using, e.g., RASMOL program, see Sayle and Milner-White (1995) TIBS 20:374-376; or Gronenberg, et 30 al. (1991) Protein Engineering 4:263-269; and other structural features are defined in Lodi, et al. (1994) Science 263:1762-1767.

35 This invention provides isolated DNA or fragments to encode a SOCS or WDS protein. In addition, this invention provides isolated or recombinant DNA which encodes a protein or polypeptide which is capable of hybridizing under appropriate conditions, e.g., high stringency, with the DNA sequences described herein. Said biologically active protein or polypeptide can be an 40 intact protein, or fragment, and have an amino acid

sequence as disclosed in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16, particularly natural embodiments. Preferred embodiments will be full length natural sequences. Further, this invention contemplates the use of isolated 5 or recombinant DNA, or fragments thereof, which encode proteins which are homologous to a SOCS or WDS protein or which were isolated using cDNA encoding a SOCS or WDS protein as a probe. The isolated DNA can have the 10 respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others. Also embraced are methods for making expression vectors with these sequences, or for making, e.g., expressing and purifying, protein products.

A DNA which codes for a SOCS or WDS protein will be 15 particularly useful to identify genes, mRNA, and cDNA species which code for related or similar proteins, as well as DNAs which code for homologous proteins from different species. There are likely homologs in other species, including primates, rodents, canines, felines, 20 and birds. Various SOCS or WDS proteins should be homologous and are encompassed herein. However, even proteins that have a more distant evolutionary relationship to the antigen can readily be isolated under appropriate conditions using these sequences if they are 25 sufficiently homologous. Primate SOCS or WDS proteins are of particular interest.

Recombinant clones derived from the genomic sequences, e.g., containing introns, will be useful for transgenic studies, including, e.g., transgenic cells and 30 organisms, and for gene therapy. See, e.g., Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) Science 244:1288; 35 Robertson (1987) (ed.) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-199.

IV. Antibodies

Antibodies can be raised to various SOCS14 or SOCS15 proteins, including individual, polymorphic, allelic, strain, or species variants, and fragments thereof, both 5 in their naturally occurring (full-length) forms and in their recombinant forms. Additionally, antibodies can be raised to SOCS or WDS proteins in either their active forms or in their inactive forms. Anti-idiotypic antibodies may also be used.

10 A. Antibody Production

A number of immunogens may be used to produce antibodies specifically reactive with SOCS or WDS proteins. Recombinant protein is the preferred immunogen for the production of monoclonal or polyclonal 15 antibodies. Naturally occurring protein may also be used either in pure or impure form. Synthetic peptides, made using the human SOCS14 or SOCS15 protein sequences described herein, may also be used as an immunogen for the production of antibodies to SOCS14 or SOCS15 proteins. 20 Recombinant protein can be expressed in eukaryotic or prokaryotic cells as described herein, and purified as described. Naturally folded or denatured material can be used, as appropriate, for producing antibodies. Either monoclonal or polyclonal antibodies may be generated for 25 subsequent use in immunoassays to measure the protein.

Methods of producing polyclonal antibodies are known to those of skill in the art. Typically, an immunogen, preferably a purified protein, is mixed with an adjuvant and animals are immunized with the mixture. The animal's 30 immune response to the immunogen preparation is monitored by taking test bleeds and determining the titer of reactivity to the SOCS or WDS protein of interest. When appropriately high titers of antibody to the immunogen are obtained, usually after repeated immunizations, blood 35 is collected from the animal and antisera are prepared. Further fractionation of the antisera to enrich for antibodies reactive to the protein can be done if desired. See, e.g., Harlow and Lane; or Coligan.

40 Monoclonal antibodies may be obtained by various techniques familiar to those skilled in the art.

Typically, spleen cells from an animal immunized with a desired antigen are immortalized, commonly by fusion with a myeloma cell (see, Kohler and Milstein (1976) Eur. J. Immunol. 6:511-519, incorporated herein by reference).

5 Alternative methods of immortalization include transformation with Epstein Barr Virus, oncogenes, or retroviruses, or other methods known in the art. Colonies arising from single immortalized cells are screened for production of antibodies of the desired 10 specificity and affinity for the antigen, and yield of the monoclonal antibodies produced by such cells may be enhanced by various techniques, including injection into the peritoneal cavity of a vertebrate host. Alternatively, one may isolate DNA sequences which encode 15 a monoclonal antibody or a binding fragment thereof by screening a DNA library from human B cells according, e.g., to the general protocol outlined by Huse, et al. (1989) Science 246:1275-1281.

Antibodies, including binding fragments and single 20 chain versions, against predetermined fragments of SOCS or WDS protein can be raised by immunization of animals with conjugates of the fragments with carrier proteins as described above. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies 25 can be screened for binding to normal or defective SOCS or WDS proteins, or screened for agonistic or antagonistic activity, e.g., effect on cell cycle progression or transcription of specific genes. These monoclonal antibodies will usually bind with at least a 30 K_D of about 1 mM, more usually at least about 300 μ M, typically at least about 10 μ M, more typically at least about 30 μ M, preferably at least about 10 μ M, and more preferably at least about 3 μ M or better.

In some instances, it is desirable to prepare 35 monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.) Lange Medical Publications, 40 Los Altos, CA, and references cited therein; Harlow and

Lane (1988) Antibodies: A Laboratory Manual CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York, NY; and particularly in Kohler and Milstein (1975) Nature

5 256:495-497, which discusses one method of generating monoclonal antibodies. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The 10 result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones, each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are 15 the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic substance.

Other suitable techniques involve selection of libraries of antibodies in phage or similar vectors.

20 See, e.g., Huse, et al. (1989) "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546. The polypeptides and 25 antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation 30 techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, 35 teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241. Also, recombinant immunoglobulins may be produced. See, Cabilly, U.S.

Patent No. 4,816,567; and Queen, et al. (1989) Proc. Nat'l Acad. Sci. USA 86:10029-10033.

The antibodies of this invention are useful for affinity chromatography in isolating SOCS or WDS protein.

5 Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, SEPHADEX, or the like, where a cell lysate or supernatant may be passed through the column, the column washed, followed by increasing concentrations of a mild

10 denaturant, whereby purified SOCS or WDS protein will be released.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled

15 with a moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies to SOCS or WDS proteins may be used for the identification of cell populations expressing the proteins. By assaying, e.g., by histology or otherwise,

20 probably a disruptive assay which kills that sample of cells, the expression products of cells expressing SOCS or WDS proteins it is possible to diagnose disease, e.g., cancerous conditions.

Antibodies raised against each SOCS or WDS protein

25 will also be useful to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the respective antigens.

30 B. Immunoassays

A particular protein can be measured by a variety of immunoassay methods. For a review of immunological and immunoassay procedures in general, see Stites and Terr (eds.) (1991) Basic and Clinical Immunology (7th ed.).

35 Moreover, the immunoassays of the present invention can be performed in many configurations, which are reviewed extensively in Maggio (ed.) (1980) Enzyme Immunoassay CRC Press, Boca Raton, Florida; Tijan (1985) "Practice and Theory of Enzyme Immunoassays," Laboratory Techniques in

Biochemistry and Molecular Biology, Elsevier Science Publishers B.V., Amsterdam; and Harlow and Lane Antibodies, A Laboratory Manual, *supra*, each of which is incorporated herein by reference. See also Chan (ed.) 5 (1987) Immunoassay: A Practical Guide Academic Press, Orlando, FL; Price and Newman (eds.) (1991) Principles and Practice of Immunoassays Stockton Press, NY; and Ngo (ed.) (1988) Non-isotopic Immunoassays Plenum Press, NY.

Immunoassays for measurement of SOCS or WDS proteins 10 can be performed by a variety of methods known to those skilled in the art. In brief, immunoassays to measure the protein can be either competitive or noncompetitive binding assays. In competitive binding assays, the sample to be analyzed competes with a labeled analyte for 15 specific binding sites on a capture agent bound to a solid surface. Preferably the capture agent is an antibody specifically reactive with SOCS or WDS proteins produced as described above. The concentration of labeled analyte bound to the capture agent is inversely 20 proportional to the amount of free analyte present in the sample.

In a competitive binding immunoassay, the SOCS or WDS protein present in the sample competes with labeled protein for binding to a specific binding agent, for 25 example, an antibody specifically reactive with the SOCS or WDS protein. The binding agent may be bound to a solid surface to effect separation of bound labeled protein from the unbound labeled protein. Alternately, the competitive binding assay may be conducted in liquid 30 phase and a variety of techniques known in the art may be used to separate the bound labeled protein from the unbound labeled protein. Following separation, the amount of bound labeled protein is determined. The amount of protein present in the sample is inversely 35 proportional to the amount of labeled protein binding.

Alternatively, a homogeneous immunoassay may be performed in which a separation step is not needed. In these immunoassays, the label on the protein is altered by the binding of the protein to its specific binding

agent. This alteration in the labeled protein results in a decrease or increase in the signal emitted by label, so that measurement of the label at the end of the immunoassay allows for detection or quantitation of the 5 protein.

Qualitative or quantitative analysis of SOCS or WDS proteins may also be determined by a variety of noncompetitive immunoassay methods. For example, a two-site, solid phase sandwich immunoassay may be used. In 10 this type of assay, a binding agent for the protein, for example an antibody, is attached to a solid support. A second protein binding agent, which may also be an antibody, and which binds the protein at a different site, is labeled. After binding at both sites on the 15 protein has occurred, the unbound labeled binding agent is removed and the amount of labeled binding agent bound to the solid phase is measured. The amount of labeled binding agent bound is directly proportional to the amount of protein in the sample.

20 Western blot analysis can be used to determine the presence of SOCS or WDS proteins in a sample. Electrophoresis is carried out, for example, on a tissue sample suspected of containing the protein. Following 25 electrophoresis to separate the proteins, and transfer of the proteins to a suitable solid support, e.g., a nitrocellulose filter, the solid support is incubated with an antibody reactive with the protein. This antibody may be labeled, or alternatively may be detected by subsequent incubation with a second labeled antibody 30 that binds the primary antibody.

The immunoassay formats described above employ labeled assay components. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide 35 variety of labels and methods may be used. Traditionally, a radioactive label incorporating ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P was used. Non-radioactive labels include proteins which bind to labeled antibodies, fluorophores, chemiluminescent agents, enzymes, and 40 antibodies which can serve as specific binding pair

members for a labeled protein. The choice of label depends on sensitivity required, ease of conjugation with the compound, stability requirements, and available instrumentation. For a review of various labeling or 5 signal producing systems which may be used, see U.S. Patent No. 4,391,904, which is incorporated herein by reference.

Antibodies reactive with a particular protein can also be measured by a variety of immunoassay methods.

10 For a review of immunological and immunoassay procedures applicable to the measurement of antibodies by immunoassay techniques, see Stites and Terr (eds.) Basic and Clinical Immunology (7th ed.) *supra*; Maggio (ed.) Enzyme Immunoassay, *supra*; and Harlow and Lane 15 Antibodies, A Laboratory Manual, *supra*.

In brief, immunoassays to measure antisera reactive with SOCS or WDS proteins can be either competitive or noncompetitive binding assays. In competitive binding assays, the sample analyte competes with a labeled 20 analyte for specific binding sites on a capture agent bound to a solid surface. Preferably the capture agent is a purified recombinant SOCS or WDS protein produced as described above. Other sources of these proteins, including isolated or partially purified naturally 25 occurring protein, may also be used. Noncompetitive assays include sandwich assays, in which the sample analyte is bound between two analyte-specific binding reagents. One of the binding agents is used as a capture agent and is bound to a solid surface. The second 30 binding agent is labeled and is used to measure or detect the resultant complex by visual or instrument means. A number of combinations of capture agent and labeled binding agent can be used. A variety of different immunoassay formats, separation techniques, and labels 35 can be also be used similar to those described above for the measurement of SOCS or WDS proteins.

V. Making SOCS or WDS proteins; Mimetics
DNAs which encode a SOCS or WDS protein or fragments
40 thereof can be obtained by chemical synthesis, screening

cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples. Methods for doing so, or making expression vectors are described herein.

5 These DNAs can be expressed in a wide variety of host cells for the synthesis of a full-length protein or fragments which can in turn, e.g., be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified molecules;

10 and for structure/function studies. Each SOCS or WDS protein or its fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. By "transformed" is meant a cell into which (or into an ancestor of which) has been

15 introduced, by means of recombinant techniques, a DNA molecule that encodes a SOCS or WDS polypeptide. Heterologously expressed SOCS or WDS polypeptides can be substantially purified to be free of protein or cellular contaminants, other than those derived from the

20 recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The antigen, e.g., SOCS or WDS protein, or portions thereof, may be expressed as fusions with other proteins or

25 possessing an epitope tag.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired antigen gene or its fragments, usually operably linked to appropriate genetic control elements that are recognized in a

30 suitable host cell. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control

35 system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that

40 terminate transcription and translation. All of the

associated elements both necessary and sufficient for the production of SOCS or WDS polypeptide will be in operable linkage with the nucleic acid encoding a SOCS or WDS polypeptide. Expression vectors also usually contain an 5 origin of replication that allows the vector to replicate independently from the host cell.

The vectors of this invention contain DNAs which encode a SOCS or WDS protein, or a fragment thereof, typically encoding, e.g., a biologically active 10 polypeptide, or protein. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing 15 eukaryotic cDNA coding for a SOCS or WDS protein in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA coding for the protein is inserted into the vector such that growth of the host containing the vector expresses 20 the cDNA in question. Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of 25 copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication 30 origin that is recognized by the host cell. It is also possible to use vectors that cause integration of a SOCS or WDS protein gene or its fragments into the host DNA by recombination, or to integrate a promoter which controls expression of an endogenous gene.

Vectors, as used herein, contemplate plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA 35 fragments into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector, but many other forms of vectors which serve an 40 equivalent function are suitable for use herein. See,

e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual Elsevier, N.Y.; and Rodriguez, et al. (eds.) (1988) Vectors: A Survey of Molecular Cloning Vectors and Their Uses Butterworth, 5 Boston, MA.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., *E. coli* and *B. subtilis*. Lower eukaryotes include yeasts, 10 e.g., *S. cerevisiae* and *Pichia*, and species of the genus *Dictyostelium*. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents. 15

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, *E. coli* and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or 20 its derivatives. Vectors that can be used to express these proteins or protein fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters 25 (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Rodriguez and Denhardt (eds.) Vectors: A Survey of Molecular Cloning Vectors and Their Uses 10:205-236

30 Buttersworth, Boston, MA.

Lower eukaryotes, e.g., yeasts and *Dictyostelium*, may be transformed with SOCS or WDS protein sequence containing vectors. For purposes of this invention, the most common lower eukaryotic host is the baker's yeast, 35 *Saccharomyces cerevisiae*. It will be used generically to represent lower eukaryotes although a number of other strains and species are also available. Yeast vectors typically consist of a replication origin (unless of the integrating type), a selection gene, a promoter, DNA

encoding the desired protein or its fragments, and sequences for translation termination, polyadenylation, and transcription termination. Suitable expression vectors for yeast include such constitutive promoters as 5 3-phosphoglycerate kinase and various other glycolytic enzyme gene promoters or such inducible promoters as the alcohol dehydrogenase 2 promoter or metallothioneine promoter. Suitable vectors include derivatives of the following types: self-replicating low copy number (such 10 as the YRp-series), self-replicating high copy number (such as the YEp-series); integrating types (such as the YIp-series), or mini-chromosomes (such as the YCp-series).

Higher eukaryotic tissue culture cells are typically 15 the preferred host cells for expression of the functionally active SOCS or WDS protein. In principle, many higher eukaryotic tissue culture cell lines may be used, e.g., insect baculovirus expression systems, whether from an invertebrate or vertebrate source. 20 However, mammalian cells are preferred to achieve proper processing, both cotranslationally and posttranslationally. Transformation or transfection and propagation of such cells is routine. Useful cell lines include HeLa cells, Chinese hamster ovary (CHO) cell 25 lines, baby rat kidney (BRK) cell lines, insect cell lines, bird cell lines, and monkey (COS) cell lines. Expression vectors for such cell lines usually include an origin of replication, a promoter, a translation initiation site, RNA splice sites (e.g., if genomic DNA 30 is used), a polyadenylation site, and a transcription termination site. These vectors also may contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or 35 retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Biol. 5:1136-1142; pMC1neo Poly-A, see Thomas, et al. (1987) Cell 51:503- 40 512; and a baculovirus vector such as pAC 373 or pAC 610.

It is likely that SOCS or WDS proteins need not be glycosylated to elicit biological responses. However, it will occasionally be desirable to express a SOCS or WDS protein polypeptide in a system which provides a specific 5 or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., in unglycosylated form, to appropriate glycosylating 10 proteins introduced into a heterologous expression system. For example, the SOCS or WDS protein gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes. It is further understood that over glycosylation may be detrimental to SOCS or WDS 15 protein biological activity, and that one of skill may perform routine testing to optimize the degree of glycosylation which confers optimal biological activity.

Furthermore, heterologously expressed proteins or polypeptides can also be expressed in plant cells. For 20 plant cells viral expression vectors (e.g., cauliflower mosaic virus and tobacco mosaic virus) and plasmid expression vectors (e.g., T1 plasmid) are suitable. Such cells are available from a wide range of sources (e.g., the American Tissue Type Culture Collection, Rockland, 25 MD; also, see for example, Ausubel, et al. (cur. ed. and Supplements; expression vehicles may be chosen from those provided e.g., in Pouwels, et al. (Cur. ed.) Cloning Vectors, A Laboratory Manual).

A SOCS or WDS protein, or a fragment thereof, may be 30 engineered to be phosphatidyl inositol (PI) linked to a cell membrane, but can be removed from membranes by treatment with a phosphatidyl inositol cleaving enzyme, e.g., phosphatidyl inositol phospholipase-C. This releases the antigen in a biologically active form, and 35 allows purification by standard procedures of protein chemistry. See, e.g., Low (1989) Biochem. Biophys. Acta 988:427-454; Tse, et al. (1985) Science 230:1003-1008; and Brunner, et al. (1991) J. Cell Biol. 114:1275-1283.

Now that SOCS or WDS proteins have been 40 characterized, fragments or derivatives thereof can be

prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and Young (1984) Solid Phase Peptide Synthesis Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis Springer-Verlag, New York, NY; and Bodanszky (1984) The Principles of Peptide Synthesis Springer-Verlag, New York, NY. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis and various forms of chromatography, and the like. The SOCS or WDS proteins of this invention can be obtained in varying degrees of purity depending upon its desired use. Purification can be accomplished by use of known protein purification techniques or by the use of the antibodies or binding partners herein described, e.g., in immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate source cells, lysates of other cells expressing the protein, or lysates or supernatants of cells producing the SOCS or WDS proteins as a result of recombinant DNA techniques, see below.

Multiple cell lines may be screened for one which expresses a SOCS or WDS protein at a high level compared with other cells. Various cell lines, e.g., a mouse thymic stromal cell line TA4, is screened and selected for its favorable handling properties. Natural SOCS or WDS proteins can be isolated from natural sources, or by

expression from a transformed cell using an appropriate expression vector. Purification of the expressed protein is achieved by standard procedures, or may be combined with engineered means for effective purification at high 5 efficiency from cell lysates or supernatants. Epitope or other tags, e.g., FLAG or His₆ segments, can be used for such purification features.

VI. Physical Variants

10 This invention also encompasses proteins or peptides having substantial amino acid sequence similarity with an amino acid sequence of a SOCS or WDS protein. Natural variants include individual, polymorphic, allelic, strain, or species variants.

15 Amino acid sequence similarity, or sequence identity, is determined by optimizing residue matches, if necessary, by introducing gaps as required. This changes when considering conservative substitutions as matches. Conservative substitutions typically include

20 substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences include natural

25 polymorphic, allelic, and interspecies variations in each respective protein sequence. Typical homologous proteins or peptides will have from 50-100% similarity (if gaps can be introduced), to 75-100% similarity (if conservative substitutions are included) over fixed

30 stretches of amino acids with the amino acid sequence of the SOCS or WDS protein. Similarity measures will be at least about 50%, generally at least 65%, usually at least 70%, preferably at least 75%, and more preferably at least 90%, and in particularly preferred embodiments, at

35 least 96% or more. See also Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison Chapter One, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics,

40 Mountain View, CA; and the University of Wisconsin

Genetics Computer Group, Madison, WI. Stretches of amino acids will be at least about 10 amino acids, usually about 20 amino acids, usually 50 amino acids, preferably 75 amino acids, and in particularly preferred embodiments 5 at least about 100 amino acids. Identity can also be measures over amino acid stretches of about 98, 99, 110, 120, 130, etc.

Nucleic acids encoding mammalian SOCS or WDS proteins will typically hybridize to the nucleic acid 10 sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, or 15 under stringent conditions. For example, nucleic acids encoding human SOCS or WDS proteins will normally hybridize to the nucleic acid of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, or 15 under stringent hybridization 15 conditions. Generally, stringent conditions are selected to be about 10° C lower than the thermal melting point (Tm) for the probe sequence at a defined ionic strength and pH. The Tm is the temperature (under defined ionic strength and pH) at which 50% of the target sequence 20 hybridizes to a perfectly matched probe. Typically, stringent conditions will be those in which the salt concentration is about 0.2 molar at pH 7 and the temperature is at least about 50° C. Other factors may significantly affect the stringency of hybridization, 25 including, among others, base composition and size of the complementary strands, the presence of organic solvents such as formamide, and the extent of base mismatching. A preferred embodiment will include nucleic acids which will bind to disclosed sequences in 50% formamide and 200 30 mM NaCl at 42° C.

Hybridizing nucleic acids to SOCS nucleic acid of the invention can be used as a cloning probe, a primer (e.g., a PCR primer), or a diagnostic probe. Hybridizing nucleic acids can be splice variants encoded by one of 35 the SOCS genes described herein. Thus, the hybridizing nucleic acids may encode a polypeptide that is shorter or longer than the various forms of SOCS described herein. Hybridizing nucleic acids may also encode proteins that are related to SOCS (e.g., polypeptides encoded by genes

that include a portion having a relatively high degree of identity to a SOCS gene described herein).

An isolated SOCS or WDS protein encoding DNA can be readily modified by nucleotide substitutions, nucleotide 5 deletions, nucleotide insertions, and short inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode SOCS or WDS protein antigens, their derivatives, or proteins having highly similar physiological, immunogenic, or antigenic 10 activity.

Modified sequences can be used to produce mutant antigens or to enhance expression. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant 15 SOCS or WDS protein derivatives include predetermined or site-specific mutations of the respective protein or its fragments. "Mutant SOCS or WDS protein" encompasses a polypeptide otherwise falling within the homology definition of the human or rodent SOCS or WDS protein as 20 set forth above, but having an amino acid sequence which differs from that of a SOCS or WDS protein as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant SOCS or 25 WDS protein" generally includes proteins having significant similarity with a protein having a sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16, e.g., natural embodiments, and as sharing various biological 30 activities, e.g., antigenic or immunogenic, with those sequences, and in preferred embodiments contain most or all of the disclosed sequence. This applies also to polymorphic variants from different individuals. Similar 35 concepts apply to different SOCS or WDS proteins, particularly those found in various warm blooded animals, e.g., mammals and birds. As stated before, it is emphasized that descriptions are generally meant to encompass other SOCS or WDS proteins, not limited to the human embodiments specifically discussed.

The invention encompasses, but is not limited to, 40 SOCS proteins and polypeptides that are functionally related to SOCS encoded by the specific sequence

identifiers of the present application. Functionally related proteins and polypeptides include any protein or polypeptide sharing a functional characteristic with SOCS of the present invention e.g., the ability to interact 5 with Janus family tyrosine kinases or the ability to be induced by IL-2 receptor activation. Such functionally related SOCS polypeptides include, but are not limited to, additions or substitutions of amino acid residues within the amino acid sequence encoded by the SOCS 10 sequences described herein which result in a silent change, thus producing a functionally equivalent SOCS polypeptide. Amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphiphatic 15 nature of the residues involved.

For example, nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine; polar neutral amino acids include glycine, serine, threonine, cysteine, 20 tyrosine, asparagine, and glutamine; positively charged (basic) amino acids include arginine, lysine, and histidine; and negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

While random mutations can be made to SOCS nucleic 25 acid (using well known random mutagenesis techniques) and the resulting SOCS polypeptides can be tested for activity, site-directed mutations of SOCS coding sequences can be engineered (using well known site-directed mutagenesis techniques) to generate mutant SOCS 30 with increased function, e.g. greater inhibition of JANUS kinase activity or greater resistance to degradation.

To design functionally related and functionally variant SOCS polypeptides, it is useful to distinguish between conserved and variable amino residues using the 35 homology comparison tables provided herein.

To preserve SOCS function, it is preferable that conserved residues remain unaltered and that the conformational folding of the SOCS functional sites be preserved. Preferably, alteration of non-conserved 40 residues are carried out with conservative alterations

e.g., a basic amino acid is replaced by a different basic amino acid. To produce altered function variants, it is preferred to make non-conservative changes at variable and or conserved residues. Deletions at conserved and 5 variable residues can also be used to create altered function variants.

Although site specific mutation sites are predetermined, mutants need not be site specific. SOCS or WDS protein mutagenesis can be conducted by making 10 amino acid insertions or deletions. Substitutions, deletions, insertions, or any combinations may be generated to arrive at a final construct. Insertions include amino- or carboxyl- terminal fusions, e.g. epitope tags. Random mutagenesis can be conducted at a 15 target codon and the expressed mutants can then be screened for the desired activity. Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis or polymerase chain reaction 20 (PCR) techniques. See also, Sambrook, et al. (1989) and Ausubel, et al. (1987 and Supplements). The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create 25 complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using segments from these proteins. A heterologous fusion protein is a fusion of proteins or segments which are 30 naturally not normally fused in the same manner e.g., a marker polypeptide or fusion partner. For example, the polypeptide can be fused to a hexa-histidine tag to facilitate purification or bacterially expressed protein or a hemagglutinin tag to facilitate purification or 35 protein expressed in eukaryotic cells. Thus, the fusion product of an immunoglobulin with a SOCS or WDS protein polypeptide is a continuous protein molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting

properties derived from each source peptide. A similar concept applies to heterologous nucleic acid sequences.

In addition, new constructs may be made from combining similar functional domains from other proteins.

5 For example, protein-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992. Thus, new chimeric polypeptides 10 exhibiting new combinations of specificities will result from the functional linkage of protein-binding specificities and other functional domains.

VII. Functional Variants

15 The blocking of physiological response to SOCS or WDS protein may result from the inhibition of binding of the protein to its binding partner, e.g., through competitive inhibition. Thus, in vitro assays of the present invention will often use isolated protein, 20 membranes from cells expressing a recombinant membrane associated SOCS or WDS protein, soluble fragments comprising binding segments of these proteins, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination 25 of the effects of either binding segment mutations and modifications, or protein mutations and modifications, e.g., protein analogs. This invention also contemplates the use of competitive drug screening assays, e.g., where neutralizing antibodies to antigen or binding partner 30 fragments compete with a test compound for binding to the protein. In this manner, the antibodies can be used to detect the presence of a polypeptide which shares one or more antigenic binding sites of the protein and can also be used to occupy binding sites on the protein that might 35 otherwise interact with a binding partner.

40 "Derivatives" of SOCS or WDS protein antigens include amino acid sequence mutants, glycosylation variants, and covalent or aggregate conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found

in SOCS or WDS protein amino acid side chains or at the N- or C- termini, by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or 5 of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of 10 alkyl-moieties including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species. Covalent attachment to carrier proteins may be important when immunogenic moieties are haptens.

In particular, glycosylation alterations are 15 included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from 20 cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid 25 residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine, or other moieties, including ribosyl groups or cross-linking reagents.

A major group of derivatives are covalent conjugates of the SOCS or WDS protein or fragments thereof with 30 other proteins or polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred protein derivatization 35 sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between SOCS or WDS protein and other homologous or heterologous proteins are also provided. Heterologous polypeptides may be fusions 40 between different surface markers, resulting in, e.g., a

hybrid protein exhibiting binding partner specificity. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions 5 of a reporter polypeptide, e.g., luciferase, with a segment or domain of a protein, e.g., a segment involved in binding partner interaction, so that the presence or location of the fused protein may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609.

10 Other gene fusion partners include bacterial β -galactosidase, *trpE*, Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816. The fusion partner can be constructed such 15 that it can be cleaved off such that a protein of substantially natural length is generated.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of 20 other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity proteins.

This invention also contemplates the use of 25 derivatives of SOCS or WDS protein other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into the three classes: (1) salts, (2) 30 side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of 35 proteinss or other binding proteins. For example, a SOCS or WDS protein antigen can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated SEPHAROSE, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or 40 without glutaraldehyde cross-linking, for use in the

assay or purification of anti-SOCS or anti-WDS protein antibodies or its respective binding partner. The SOCS or WDS protein can also be labeled with a detectable group, e.g., radioiodinated by the chloramine T

5 procedure, covalently bound to rare earth chelates, or conjugated to another fluorescent moiety for use in diagnostic assays. Purification of SOCS or WDS proteins may be effected by immobilized antibodies or binding partner.

10 Isolated SOCS or WDS protein genes will allow transformation of cells lacking expression of corresponding SOCS or WDS protein, e.g., either species types or cells which lack corresponding proteins and exhibit negative background activity. Expression of

15 transformed genes will allow isolation of antigenically pure cell lines, with defined or single species variants. This approach will allow for more sensitive detection and discrimination of the physiological effects of SOCS or WDS binding proteins. Subcellular fragments, e.g.,

20 cytoplasts or membrane fragments, can be isolated and used.

VIII. Binding Agent:SOCS or :WDS Protein Complexes

A SOCS or WDS protein that specifically binds to or

25 that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16 is typically determined in an immunoassay. The immunoassay uses a polyclonal

30 antiserum which was raised to a protein of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, or 16. This antiserum is selected to have low crossreactivity against other intracellular regulatory proteins and any such crossreactivity is removed by immunoabsorption prior to use in the

35 immunoassay.

In order to produce antisera for use in an immunoassay, the protein of desired sequence, e.g., SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, and/or 16, is isolated as described herein. For example, recombinant protein may

40 be produced in a mammalian cell line. An inbred strain

of mice such as Balb/c is immunized with the protein of appropriate sequence using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, *supra*). Alternatively, a 5 synthetic peptide, preferably near full length, derived from the sequences disclosed herein and conjugated to a carrier protein can be used an immunogen. Polyclonal sera are collected and titered against the immunogen protein in an immunoassay, for example, a solid phase 10 immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of 10^4 or greater are selected and tested for their cross reactivity against other intracellular proteins, using a 15 competitive binding immunoassay such as the one described in Harlow and Lane, *supra*, at pages 570-573. Preferably two intracellular proteins are used in this determination in conjunction with the desired SOCS or WDS protein.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For 20 example, a protein of SEQ ID NO: 2 or 4 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the 25 immobilized protein is compared to the protein of SEQ ID NO: 2 or 4. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with 30 each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorbtion with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used 35 in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the SOCS14 or SOCS15 protein of SEQ ID NO: 2 and 6, or 4). In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to 40 inhibit 50% of the binding of the antisera to the

immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein, e.g., of SEQ ID NO: 2 that is required, then the second protein is said to specifically bind to an 5 antibody generated to the immunogen.

It is understood that each of SOCS or WDS proteins are members of respective families of homologous proteins that comprise two or more genes. For a particular gene product, such as the human SOCS14 or SOCS15 protein, the 10 term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are polymorphic, allelic, non-allelic, or species variants. It is also understood that the term "SOCS14 or SOCS15 protein" includes nonnatural mutations introduced by 15 deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding SOCS14 or SOCS15 proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations should substantially 20 maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring SOCS or WDS protein, for example, the human SOCS14 or SOCS15 protein 25 shown in SEQ ID NO: 2 and 6, or 4 and 8. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring, e.g., a proliferative effect. Particular protein modifications considered minor would include 30 conservative substitution of amino acids with similar chemical properties, as described above for the SOCS14 or SOCS15 protein as a whole. By aligning a protein optimally with the protein of SEQ ID NO: 2, 4, 6, or 8, and by using the conventional immunoassays described 35 herein to determine immunoidentity, or by using proliferative assays, one can determine the protein compositions of the invention.

IX. Uses

The present invention provides reagents which will find use in diagnostic applications as described elsewhere herein, e.g., in the general description for 5 developmental abnormalities, or below in the description of kits for diagnosis. Moreover, the SOCS proteins can block signaling via cytokine receptors.

10 SOCS or WDS nucleotides, e.g., human SOCS14 or SOCS15 DNA or RNA, may be used as a component in a forensic assay. For instance, the nucleotide sequences provided may be labeled using, e.g., ^{32}p or biotin and used to probe standard restriction fragment polymorphism blots, providing a measurable character to aid in 15 distinguishing between individuals. Such probes may be used in well-known forensic techniques such as genetic fingerprinting. In addition, nucleotide probes made from SOCS or WDS sequences may be used in *in situ* assays to detect chromosomal abnormalities. For instance, 20 rearrangements in the human chromosome encoding a SOCS14 or SOCS15 gene may be detected via well-known *in situ* techniques, using SOCS14 or SOCS15 probes in conjunction with other known chromosome markers.

25 Antibodies and other binding agents directed towards SOCS or WDS proteins or nucleic acids may be used to purify the corresponding SOCS or WDS molecule. As described in the Examples below, antibody purification of SOCS or WDS protein components is both possible and practicable. Antibodies and other binding agents may also be used in a diagnostic fashion to determine whether 30 SOCS or WDS protein components are present in a tissue sample or cell population using well-known techniques described herein. The ability to attach a binding agent to a SOCS or WDS protein provides a means to diagnose disorders associated with SOCS or WDS protein 35 misregulation. Antibodies and other SOCS or WDS protein binding agents may also be useful as histological markers. It is likely that specific SOCS or WDS protein expression is limited to specific tissue types. By directing a probe, such as an antibody or nucleic acid to 40 a SOCS14 or SOCS15 protein it is possible to use the

probe to distinguish tissue and cell types *in situ* or *in vitro*.

This invention also provides reagents with significant therapeutic value. The SOCS or WDS protein (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to a SOCS or WDS protein, are useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or degenerative conditions. Abnormal proliferation, regeneration, degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by a SOCS or WDS protein is a target for an agonist or antagonist of the protein. The proteins likely play a role in regulation or development of neuronal or hematopoietic cells, e.g., lymphoid cells, which affect immunological responses.

For example, SOCS or WDS proteins likely play a role in T cell activation deficiencies in which patients develop clinical manifestations of T cell immunodeficiency such as opportunistic infections, recurrent viral or bacterial infections, diarrhea, autoimmune hemolytic anemia, lymphoid hepatitis and dermatitis, and Hodgkin lymphoma, at various stages of childhood. An excess of SOCS proteins might lead to SCID-like (severe combined immunodeficiencies) syndromes while a deficit of SOCS or WDS proteins may lead to malignant growth, for example, adult T cell leukemia/lymphoma is a disease associated with uncontrolled T-cell proliferation and is correlated at the molecular level with the presence of the IL-2 receptor (Schechter, G.P.; "Chronic Lymphocytic Leukemia" in Clinical Immunology: Principles and Practice, Rich (ed.) Mosby, St. Louis (Curr. ed.)). A model for adult T cell leukemia suggests that the disease may result from constitutive activation of the IL-2 receptor and its subsequent constitutive signaling cascade.

Administration of exogenous SOCS to effected T cells may modulate this disease.

Other abnormal developmental conditions are known in cell types shown to possess SOCS or WDS protein mRNA by 5 northern blot analysis. See Berkow (ed.) The Merck Manual of Diagnosis and Therapy, Merck & Co., Rahway, N.J.; Thorn et al. Harrison's Principles of Internal Medicine, McGraw-Hill, N.Y.; and Rich (ed.) Clinical Immunology: Principles and Practice, Mosby, St. Louis 10 (Curr. ed.). Developmental or functional abnormalities, e.g., of the neuronal or immune system, cause significant medical abnormalities and conditions which may be susceptible to prevention or treatment using compositions provided herein.

15 Recombinant SOCS or WDS protein or SOCS or WDS antibodies can be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers or 20 diluents, e.g., immunogenic adjuvants, along with physiologically innocuous stabilizers and excipients. These combinations can be sterile filtered and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This 25 invention also contemplates use of antibodies or binding fragments thereof, including forms which are not complement binding.

30 Drug screening using antibodies or fragments thereof can identify compounds having binding affinity to SOCS or WDS protein, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the protein. 35 Likewise, a compound having intrinsic stimulating activity can activate the binding partner and is thus an agonist in that it simulates the activity of a SOCS or WDS protein. This invention further contemplates the therapeutic use of antibodies to SOCS or WDS protein as

antagonists. This approach should be particularly useful with other SOCS or WDS protein species variants.

Another therapeutic approach included within the invention involves direct administration of reagents or compositions by any conventional administration techniques (for example but not restricted to local injection, inhalation, or administered systemically), to the subject with an immune, allergic or trauma disorder. The reagents, formulations or compositions included within the bounds and metes of the invention may also be targeted to specific cells by any of the methods described herein. The actual dosage of reagent, formulation or composition that modulates an immune, disorder depends on many factors, including the size and health of an organism, however one of one of ordinary skill in the art can use the following teachings describing the methods and techniques for determining clinical dosages. Spilker (1984) Guide to Clinical Studies and Developing Protocols, Raven Press Books, Ltd., New York, pp. 7-13, 54-60; Spilker (1991) Guide to Clinical Trials, Raven Press, Ltd., New York, pp. 93-101; Craig and Stitzel (eds. 1986) Modern Pharmacology, 2d ed., Little, Brown and Co., Boston, pp. 127-33; Speight (ed. 1987) Avery's Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics, 3d ed., Williams and Wilkins, Baltimore, pp. 50-56; Tallarida, et al. (1988) Principles in General Pharmacology, Springer-Verlag, New York, pp. 18-20) to determine the appropriate dosage to use; but, generally, in the range of about between 0.5 fg/ml and 500 μ g/ml inclusive final concentration are administered per day to an adult in any pharmaceutically-acceptable carrier.

The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, physiological state of the patient, and other medicants administered. Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used *in vitro* may provide useful guidance in the amounts useful for *in situ* administration of these reagents.

Animal testing of effective doses for treatment of particular disorders will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and (1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA. Methods for administration are discussed therein and below, e.g., for oral, intravenous, 10 intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, NJ. Dosage ranges would ordinarily 15 be expected to be in amounts lower than 1 mM concentrations, typically less than about 10 μ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with an 20 appropriate carrier. Slow release formulations, or a slow release apparatus will often be utilized for continuous administration.

SOCS or WDS protein, fragments thereof, and 25 antibodies to it or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be 30 administered in any conventional dosage formulation. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers 35 thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for 40 oral, rectal, nasal, or parenteral (including

subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g.,
5 Gilman, et al. (eds.) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics (8th ed.) Pergamon Press; and (1990) Remington's Pharmaceutical Sciences (17th ed.) Mack Publishing Co., Easton, PA; Avis, et al. (eds.) (1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds.) (1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association
10 with other therapeutic agents.

Both the naturally occurring and the recombinant forms of the SOCS or WDS proteins of this invention are particularly useful in kits and assay methods which are capable of screening compounds for binding activity to
20 the proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds in a short period. See, e.g., Fodor, et al. (1991) Science 251:767-773, and other descriptions of chemical diversity libraries, which
25 describe means for testing of binding affinity by a plurality of compounds. The development of suitable assays can be greatly facilitated by the availability of large amounts of purified, soluble SOCS or WDS protein as provided by this invention.

30 For example, antagonists can normally be found once the protein has been structurally defined. Testing of potential protein analogs is now possible upon the development of highly automated assay methods using a purified binding partner. In particular, new agonists
35 and antagonists will be discovered by using screening techniques described herein. Of particular importance are compounds found to have a combined binding affinity for multiple SOCS or WDS protein binding components, e.g., compounds which can serve as antagonists for
40 species variants of a SOCS or WDS protein.

This invention is particularly useful for screening compounds by using recombinant protein in a variety of drug screening techniques. The advantages of using a recombinant protein in screening for specific binding 5 partners include: (a) improved renewable source of the SOCS or WDS protein from a specific source; (b) potentially greater number of binding partners per cell giving better signal to noise ratio in assays; and (c) species variant specificity (theoretically giving greater 10 biological and disease specificity).

One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing a SOCS or WDS protein binding counterpart. Cells may be isolated which 15 express a binding counterpart in isolation from any others. Such cells, either in viable or fixed form, can be used for standard protein binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which 20 describe sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of SOCS14 or SOCS15 protein) are contacted and incubated with a labeled binding partner or antibody having known binding affinity to the protein, such as 25 ¹²⁵I-antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of protein binding. The amount of test compound bound is inversely proportional to the 30 amount of labeled binding partner binding to the known source. Any one of numerous techniques can be used to separate bound from free protein to assess the degree of protein binding. This separation step could typically involve a procedure such as adhesion to filters followed 35 by washing, adhesion to plastic followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on SOCS or WDS protein mediated functions, e.g., second messenger levels, i.e., cell proliferation; inositol phosphate pool 40 changes, transcription using a luciferase-type assay; and

others. Some detection methods allow for elimination of a separation step, e.g., a proximity sensitive detection system.

Another method utilizes membranes from transformed 5 eukaryotic or prokaryotic host cells as the source of a SOCS or WDS protein. These cells are stably transformed with DNA vectors directing the expression of a SOCS or WDS protein, e.g., an engineered membrane bound form. Essentially, the membranes would be prepared from the 10 cells and used in a protein binding assay such as the competitive assay set forth above.

Still another approach is to use solubilized, unpurified or solubilized, purified SOCS or WDS protein from transformed eukaryotic or prokaryotic host cells. 15 This allows for a "molecular" binding assay with the advantages of increased specificity, the ability to automate, and high drug test throughput.

Another technique for drug screening involves an 20 approach which provides high throughput screening for compounds having suitable binding affinity to a SOCS or WDS protein antibody and is described in detail in Geysen, European Patent Application 84/03564, published on September 13, 1984. First, large numbers of different 25 small peptide test compounds are synthesized on a solid substrate, e.g., plastic pins or some other appropriate surface, see Fodor, et al., *supra*. Then all the pins are reacted with solubilized, unpurified or solubilized, purified SOCS or WDS protein antibody, and washed. The next step involves detecting bound SOCS or WDS protein 30 antibody.

Rational drug design may also be based upon 35 structural studies of the molecular shapes of the SOCS or WDS protein and other effectors or analogs. See, e.g., Methods in Enzymology vols 202 and 203. Effectors may be other proteins which mediate other functions in response to protein binding, or other proteins which normally interact with the binding partner. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. 40

These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography

5 Academic Press, NY.

A purified SOCS or WDS protein can be coated directly onto plates for use in the aforementioned drug screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture 10 antibodies to immobilize the respective protein on the solid phase.

X. Kits

This invention also contemplates use of SOCS or WDS 15 proteins, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of SOCS or WDS protein or a binding partner. Typically the kit will have a compartment containing either a defined SOCS or WDS 20 protein peptide or gene segment or a reagent which recognizes one or the other, e.g., binding partner fragments or antibodies.

A kit for determining the binding affinity of a test compound to a SOCS or WDS protein would typically 25 comprise a test compound; a labeled compound, e.g., a binding agent or antibody having known binding affinity for the SOCS or WDS protein; a source of SOCS or WDS protein (naturally occurring or recombinant); and a means for separating bound from free labeled compound, such as 30 a solid phase for immobilizing the SOCS or WDS protein. Once compounds are screened, those having suitable binding affinity to the SOCS or WDS protein can be evaluated in suitable biological assays, as are well known in the art, to determine whether they act as 35 agonists or antagonists to the binding partner. The availability of recombinant SOCS or WDS protein polypeptides also provide well defined standards for calibrating such assays.

A preferred kit for determining the concentration 40 of, for example, a SOCS or WDS protein in a sample would

typically comprise a labeled compound, e.g., binding partner or antibody, having known binding affinity for the SOCS or WDS protein, a source of SOCS or WDS protein (naturally occurring or recombinant), and a means for 5 separating the bound from free labeled compound, for example, a solid phase for immobilizing the SOCS or WDS protein. Compartments containing reagents, and instructions, will normally be provided.

Antibodies, including antigen binding fragments, 10 specific for the SOCS or WDS protein or fragments thereof are useful in diagnostic applications to detect the presence of elevated levels of SOCS or WDS protein and/or its fragments. Such diagnostic assays can employ lysates, live cells, fixed cells, immunofluorescence, 15 cell cultures, body fluids, and further can involve the detection of antigens related to the protein in serum, or the like. Diagnostic assays may be homogeneous (without a separation step between free reagent and antigen-SOCS or -WDS protein complex) or heterogeneous (with a 20 separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA), and 25 the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to a SOCS or WDS protein or to a particular fragment thereof. Similar assays have also been extensively discussed in the literature. See, 30 e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press, NY; Chan (ed.) (1987) Immunoassay: A Practical Guide Academic Press, Orlando, FL; Price and Newman (eds.) (1991) Principles and Practice of Immunoassay Stockton Press, NY; and Ngo (ed.) (1988) Nonisotopic Immunoassay Plenum Press, NY.

Anti-idiotypic antibodies may have similar use to 35 diagnose presence of antibodies against a SOCS or WDS protein, as such may be diagnostic of various abnormal states. For example, overproduction of SOCS or WDS 40 protein may result in production of various immunological

or other medical reactions which may be diagnostic of abnormal physiological states, e.g., in cell growth, activation, or differentiation.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody or binding partner, or labeled SOCS or WDS protein is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent. Desirably, the reagents are provided as a dry lyophilized powder, where the reagents may be reconstituted in an aqueous medium providing appropriate concentrations of reagents for performing the assay.

Many of the aforementioned constituents of the drug screening and the diagnostic assays may be used without modification, or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In any of these assays, the protein, test compound, SOCS or WDS protein, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as ^{125}I , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free protein, or alternatively the bound from the free test compound. The SOCS or WDS protein can

be immobilized on various matrices followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the SOCS or WDS protein to a matrix include, without limitation, 5 direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of protein/binding partner or antigen/antibody complex by any of several methods including those utilizing, e.g., 10 an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30:1457-1461, and the 15 double antibody magnetic particle separation as described in U.S. Pat. No. 4,659,678.

Methods for linking proteins or their fragments to the various labels have been extensively reported in the literature and do not require detailed discussion here. 20 Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated 25 olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of a SOCS or WDS protein. These 30 sequences can be used as probes for detecting levels of the SOCS or WDS protein message in samples from natural sources, or patients suspected of having an abnormal condition, e.g., cancer or developmental problem. The preparation of both RNA and DNA nucleotide sequences, the 35 labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes 40 may be up to several kilobases. Various labels may be

employed, most commonly radionuclides, particularly ^{32}P . However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for 5 binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorophores, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA 10 hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected. The use of 15 probes to the novel anti-sense RNA may be carried out using many conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes 20 amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the 25 combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

The broad scope of this invention is best understood 30 with reference to the following examples, which are not intended to limit the invention to specific embodiments.

EXAMPLES

I. General Methods

5 Many of the standard methods below are described or referenced, e.g., in Maniatis, et al. (Cur. ed..) Molecular Cloning, A Laboratory Manual Cold Spring Harbor Laboratory, Cold Spring Harbor Press, NY; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d 10 ed.) Vols. 1-3, CSH Press, NY; Ausubel, et al., Biology Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology Wiley/Greene, NY; Innis, et al. (eds.) (1990) PCR Protocols: A Guide to Methods and Applications

15 Academic Press, NY. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Deutscher (1990) "Guide to Protein Purification," Methods in Enzymology vol. 182, and other volumes in this series; Coligan, et al. (1995 and supplements) Current Protocols in Protein Science John Wiley and Sons, New York, NY; P. Matsudaira (ed.) (1993) A Practical Guide to Protein and Peptide

20 25 Purification for Microsequencing, Academic Press, San Diego, CA; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, NJ, or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments (epitope tags), e.g., to a FLAG sequence or an equivalent which can be fused, e.g., via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in 30 Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, NY; and Crowe, et al. (1992) OIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

35 Standard immunological techniques are described, 40 e.g., in Hertzenberg, et al. (eds. 1996) Weir's Handbook

of Experimental Immunology vols 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Methods in Enzymology volumes. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163. Assays for neural cell biological activities are described, e.g., in Wouterlood (ed. 1995) Neuroscience Protocols modules 10, Elsevier; Methods in Neurosciences Academic Press; and Neuromethods Humana Press, Totowa, NJ. Methodology of developmental systems is described, e.g., in Meissami (ed.) Handbook of Human Growth and Developmental Biology CRC Press; and Chrispeels (ed.) Molecular Techniques and Approaches in Developmental Biology Interscience.

FACS analyses are described in Melamed, et al. (1990) Flow Cytometry and Sorting Wiley-Liss, Inc., New York, NY; Shapiro (1988) Practical Flow Cytometry Liss, New York, NY; and Robinson, et al. (1993) Handbook of Flow Cytometry Methods Wiley-Liss, New York, NY.

20 II. Isolation of full length SOCS or WDS clones
Standard methods are used to isolate full length genes. A cDNA library from an appropriate, e.g., human, cell, preferably a STAT containing cell type. The appropriate sequence is selected, and hybridization at high stringency conditions is performed to find a full length corresponding gene. It is noted that the mouse and human protein sequences are virtually identical.

30 III. Isolation of primate SOCS14 or SOCS15 clones
The full length, or appropriate fragments, of human genes are used to isolate a corresponding monkey or other primate gene. Preferably a full length coding sequence is used for hybridization. Similar source materials as indicated above are used to isolate natural genes, including genetic, polymorphic, allelic, or strain variants. Other species variants are also isolated using similar methods.

IV. Isolation of an avian SOCS14 or SOCS15 clone

An appropriate avian source is selected as above.

Similar methods are utilized to isolate a species variant, though the level of similarity will typically be 5 lower for avian protein as compared to a human to mouse sequence.

V. Expression; purification; characterization

10 Proteins of interest are immunoprecipitated and affinity purified as described above, e.g., from a natural or recombinant source.

Alternatively, with an appropriate clone from above, the coding sequence is inserted into an appropriate expression vector. This may be in a vector specifically 15 selected for a prokaryote, yeast, insect, or higher vertebrate, e.g., mammalian expression system. Standard methods are applied to produce the gene product, preferably as a soluble secreted molecule, but will, in certain instances, also be made as an intracellular 20 protein. Intracellular proteins typically require cell lysis to recover the protein, and insoluble inclusion bodies are a common starting material for further purification.

With a clone encoding a vertebrate SOCS14 or SOCS15 25 protein, recombinant production means are used, although natural forms may be purified from appropriate sources. The protein product is purified by standard methods of protein purification, in certain cases, e.g., coupled with immunoaffinity methods. Immunoaffinity methods are 30 used either as a purification step, as described above, or as a detection assay to determine the separation properties of the protein.

35 Preferably, the protein is secreted into the medium, and the soluble product is purified from the medium in a soluble form. Alternatively, as described above, inclusion bodies from prokaryotic expression systems are a useful source of material. Typically, the insoluble protein is solubilized from the inclusion bodies and refolded using standard methods. Purification methods 40 are developed as described above.

The product of the purification method described above is characterized to determine many structural features. Standard physical methods are applied, e.g., amino acid analysis and protein sequencing. The 5 resulting protein is subjected to CD spectroscopy and other spectroscopic methods, e.g., NMR, ESR, mass spectroscopy, etc. The product is characterized to determine its molecular form and size, e.g., using gel chromatography and similar techniques. Understanding of 10 the chromatographic properties will lead to more gentle or efficient purification methods.

Prediction of glycosylation sites may be made, e.g., as reported in Hansen, et al. (1995) Biochem. J. 308:801-813. However, as intracellular proteins, they are 15 unlikely to be normally glycosylated.

The purified protein is also be used to identify other binding partners of SOCS or WDS as described, e.g., in Fields and Song (1989) Nature 340:245-246.

20 VI. Preparation of antibodies against vertebrate SOCS or WDS

With protein produced, as above, animals are immunized to produce antibodies. Polyclonal antiserum is raised using non-purified antigen, though the resulting 25 serum will exhibit higher background levels. Preferably, the antigen is purified using standard protein purification techniques, including, e.g., affinity chromatography using polyclonal serum indicated above. Presence of specific antibodies is detected using defined 30 synthetic peptide fragments.

35 Polyclonal serum is raised against a purified antigen, purified as indicated above, or using, e.g., a plurality of, synthetic peptides. A series of overlapping synthetic peptides which encompass all of the full length sequence, if presented to an animal, will produce serum recognizing most linear epitopes on the protein. Such an antiserum is used to affinity purify protein, which is, in turn, used to introduce intact full length protein into another animal to produce another 40 antiserum preparation.

Similar techniques are used to generate induce monoclonal antibodies to either unpurified antigen, or, preferably, purified antigen.

5 VII. Cellular and tissue distribution

Distribution of the protein or gene products are determined, e.g., using immunohistochemistry with an antibody reagent, as produced above, by Western blotting of cell lysates, or by screening for nucleic acids 10 encoding the respective protein. Either hybridization or PCR methods are used to detect DNA, cDNA, or message content. Histochemistry allows determination of the specific cell types within a tissue which express higher or lower levels of message or DNA. Antibody techniques 15 are useful to quantitate protein in a biological sample, including a liquid or tissue sample. Immunoassays are developed to quantitate protein. Also FACS analysis may be used to evaluate expression in a cell population. Appropriate tissue samples or cell types are isolated and 20 prepared for such detection. Commercial tissue blots are available, e.g., from Clontech (Mountain View, CA). Alternatively, cDNA library Southern blots can be analyzed.

25 VIII. STAT interference by SOCS or WDS proteins

Standard methods for testing the biological activity of the SOCS gene products in STAT signaling are described, e.g., in Starr, et al. (1997) *Nature* 387:917-921; Endo, et al. (1997) *Nature* 387:921-924; and Naka, et 30 al. *Nature* 387:924-929. Alternatively, JAK/STATs are necessary for signal transduction. This assay is performed as described, e.g., in Ho, et al. (1995) *Mol. Cell. Biol.* 15:5043-5-53, and blockage with these gene products may be tested.

35 In particular, the STAT5 dependent signaling in response to IL-2 is inhibited by the SOCS family member SOCS3.

IX. Antagonists of SOCS function

The inhibition of SOCS function may be effected by inhibitors of the specific interaction of these gene products and their respective STAT molecules. With the 5 information on the specificity of pairings between these SOCS and respective STAT family members, compound libraries may be screened for blockage of such interactions. Thus, inhibitory action of the SOCS may be blocked with small molecule drug candidates.

10 Methods of using gene therapy are described, e.g., in Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology, Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) 15 Science 244:1288; Robertson (1987) (ed.) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach, IRL Press, Oxford; and Rosenberg (1992) J. Clinical Oncology 10:180-189. Also included is the use of antisense RNA in gene therapy to block expression of the target gene, or 20 proper splicing of gene transcripts.

X. Comparison of various SOCS embodiments

Tables 1 and 2 show comparison of various SOCS or WDS embodiments. Table 1 shows comparisons of the 25 relevant portions of the gene products, particularly in the region of SOCS14 from Met168 to Leu293.

Table 2 shows alignment of the WDS "SOCSBOX protein" with a consensus of the mouse and human SOCS15 (WDS11) protein sequences, which are identical. See GenBank 30 Accession numbers U88325; U88326; U88327; U88328; AB000676; AB000677; AB000710. This is aligned with the new WDS12, SEQ ID NO: 16.

Table 1: Comparison of various SOCS family members. mCIS is SEQ ID NO: 15; hSOCS1 IS SEQ ID NO: 16; mSOCS1 is SEQ ID NO: 17; hSOCS2 is SEQ ID NO: 18; hSOCS3 is SEQ ID NO: 19; mSOCS3 is SEQ ID NO: 20; and human SOCS16 is SEQ ID NO: 21.

5	mCIS		
	hSOCS1		
	mSOCS1		
	hSOCS2		
10	hSOCS3		
	mSOCS3		
	hSOCS14		MEVRVKALVHSSS
	mSOCS17	AELGEIR-----	PESAQKQLPLRKA
	hSOCS18	MDKVGKMWNNLKYRCQNLFSHEGGSRNENVEMNPNCPCSVKEKSTISLGEA	
15	hSOCS19	ERGLETNSCSEEELSSPGRGGGGGRLLLQ	
	mCIS		
	hSOCS1		
20	mSOCS1		
	hSOCS2	ALSPAATLTAWPADSARRGP-----	
	hSOCS3		
	mSOCS3		
	hSOCS14	PSPALNGVRKDFHDLQSETTCQEQAANSLKSSASHNGDLHLHLDHVVPVVI	
25	mSOCS17	EN-----TIFITILEVKNLFKMAENNNSKNVDRPKTSRSRSAD-	
	hSOCS18	APQQESSPLRENVALQLGLSPSKTFSRRNNAEIPQVVEISIEKDSDS	
	hSOCS19	PPGPELPPVFFPLQDVLVPLGRLSRGEQQQQQQQPPPPPPGPLRPLAG	
	mCIS		
	hSOCS1		
30	mSOCS1		
	hSOCS2	-----	
	hSOCS3		
35	mSOCS3		
	hSOCS14	G-----LMPQDYIYQYTVPDDEGMYPLEGSR-----	
	mSOCS17	-----RKD-----GYVWSGKK-----LWSKKSESCSESEAKKG-----	
	hSOCS18	GATPGTRILARRDSYSRHPWGKKKHSCTKTQSSLDEKKPGRTRSGLQ	
	hSOCS19	-----PSRKGSFKIRLSRLFRTKSCNGSGG-----	
40	mCIS		MVLCVQG
	hSOCS1		
	mSOCS1		
45	hSOCS2	-----GCTASGYPVPAARA-PAAGDQWVT--AAARDFVIR--PPGSGEKE	
	hSOCS3		
	mSOCS3		
	hSOCS14	-----YCLDSSSPMEVSAPPQVGGRAFPEDESQVDQDLVVAPEIFVDQS	
	mSOCS17	----QLCSSIELDLDHSCG-HRFLGRSLK--QLQDAVGQCFPIKNCGR	
50	hSOCS18	RRERRYYGVSSMQDMDSVSS-RAVGSRSLR--ORLQDTVGLCFPMRTYSKQ	
	hSOCS19	---GDGTGKRPSGELAAS-AASLTDGG--SAGRELDAGRKPKLRTQ	

Table 1 (continued):

5	mCIS	SCPLLAVEQIGRR-PLWAQSLELPGPA-----	-MQPLPTGA--
	hSOCS1	MVAHNQVAADN-----	-AVSTAEEPR-----
	mSOCS1	MVARNQVAADN-----	-AISPAEEPR-----
	hSOCS2	PHPFSLCHHFHGPAGLVLGFALTSRKD-----	-ANPSLTPARAAT-----
	hSOCS3	MVTHSKFPAAAG-----	-MSRPLDTS-----
	mSOCS3	MVTHSKFPAAAG-----	-MSRPLDTS-----
10	hSOCS14	VNGLLIGTTGVMLQSPRAGHDVPPPLS-----	-PLLPPNQNNQ-----
	mSOCS17	HSPGLPSKRKIHISLMDXCFPPRSDLAFRWHIFKRTVPMSPNS-----	
	hSOCS18	SKPLFSNKRKIHISLMLKEKCPFPAGSDLAQKWHLIKQHTAPVSPHSTTF-----	
	hSOCS19	AFSPVFSPLFTGETVSLVDVDISQRG-----	-LTSPHPPTP-----
15	mCIS	-	-
	hSOCS1	-----RRPE-----	-PSSSSSSS-----PAA
	mSOCS1	-----RRSE-----	-PSSSSSSS-----PAA
	hSOCS2	-----CLCRGD-----	-PS-----LMTLR
	hSOCS3	-----R-----	
20	mSOCS3	-----R-----	
	hSOCS14	-----IQRNFS-----	-GLT
	mSOCS17	-----DEWVSAADLSERKLRDAQLKRRNTTEDDIPCFSHNTGQPCVITANS-----	
	hSOCS18	DTFDPLSVLSTEDDEEDRLRERRRLSIEGVDPDPPNAQIHTEATAQVNPLF-----	
	hSOCS19	-----PPPPRRSLSLDDISGTLPTSVLVAQMGSSLQSFPLP-----	
25	mCIS	-FPFEEVTEETPVQAENE-----	-PKVLDP-----
	hSOCS1	PARPRPCPAVPAPAPGD-----	-THFRTRFS-----
	mSOCS1	PVRPRPCPAVPAPAPGD-----	-THFRTRFS-----
30	hSOCS2	CLEPSGNGGEETRSQNG-----	-TAGSAEPP-----
	hSOCS3	-----	-LKTFFS-----
	mSOCS3	-----	-LKTFFS-----
	hSOCS14	GTEAHVAESMRCHLNF-----	-PNSAPGVARVIDSQV-----
	mSOCS17	CTGGHITGSMMLVTNN-SIEDSDMSDEEIITLCTSSRKRNKPR--WEM-----	
35	hSOCS18	KLGPKLAPGMTEISGDSSAIQQANCDSEEDTTLCLQSR-RQKQRQISGD-----	
	hSOCS19	PPPPPHAPDAFPRIAPIR-----	-AAESLHSQPP-----
40	mCIS	-----EGDLCIAKTFSYLRES-----	-GWYWGWSITASEAROHQ
	hSOCS1	-----HADYRRITRASALLDAC-----	-GFWGPLSVRGAHERLR
	mSOCS1	-----HSDYRRITRASALLDAC-----	-GFWGPLSVRGAHERLR
	hSOCS2	-----SPQARLAKALRELGOT-----	-GWYWGSMTVNEAKEKLL
	hSOCS3	-----KSEYQLVUNAVRKQLES-----	-GFWWSAVTGGEANLLS
	mSOCS3	-----KSEYQLVUNAVRKQLES-----	-GFWWSAVTGGEANLLS
45	hSOCS14	-----SSGPMVTSLTEELKKLAKQGWYWPITRWEAECKLA	
	mSOCS17	EEEILQLEAPPKFTQIDYVHCLVPDLQISNNPCYWGMDKYAAEALLE-----	
	hSOCS18	SHTHVSRQGAWKVHTQIDYIHCCLVPDLQITGNPCYWGMDRYEAELSE-----	
	hSOCS19	-----QHLQCPLYRDPSSFAASLRELEKC-----	-GWYWGPMNWEDAEMKLK
		* * * *	

Table 1 (continued):

	mCIS	KMPEGTFLVLDST--HPSYLFVLSVKTTRGPTNVRLEYADSSFRLDNSNCLS
5	hSOCS1	AEPVGTFVLRDSR--QRNCFFALSVKMASGPTSIRVHFQAGRFLHDGS-R-
	mSOCS1	AEPVGTFVLRDSR--QRNCFFALSVKMASGPTSIRVHFQAGRFLHDGS-R-
	hSOCS2	EAPEGTFLIRDSS--HSDYLLTISVKT'SAGPTNLRLEYQDGKFRLDSTICV
	hSOCS3	AEPAAGTFLIRDSSDQR--HFFALSVKTQSGTKNLRQCECGGSFSLQSDPRS
	mSOCS3	AEPAAGTFLIRDSSDQR--HFFALSVKTQSGTKNLRQCECGGSFSLQSDPRS
10	hSOCS14	NVPDGSFLVLDSS--DDRYLLSSLFRSHGKTLHTRIEHSNGRFSFYEQPD-
	mSOCS17	GKPEGTFLLRDSA--QEDYLFVSFSRSLHARIEQWNHNFSDAHDPA-
	hSOCS18	GKPEGTFLLRDSA--QEDYLFVSFSAAATTGSLHARIEQWNHNFSDAHDPA-
	hSOCS19	GKPDGSFLVLDSS--DPRYILSSLFRSQRSGITHHTRMEHYRTFSLWCHPKF
		* * . * * . * . * . *
15	mCIS	RP-RILAFPDVVSUVQHYVVASCAADTRSDSPDPAFTPALPMSKQDAPSDS
	hSOCS1	-----ESFDCLFELLEHYVAAP-----RMLG
	mSOCS1	-----ETFDCLFELLEHYVAAP-----RMLG
	hSOCS2	KS-KLKQFDHSVHLIDYYVQMCKDK-----RTGPEAPRNG
	hSOCS3	TQ-PVPRFDCVVLVLYHHYMPPPGAPSFP--SPPTEPSSVEPEQPSAQALPG
20	mSOCS3	TQ-PVPRFDCVVLVLYHHYMPPPGAPSFS--LPPTEFSSVEPEQPPAQALPG
	hSOCS14	-----VERTYSTVLDLIEHSIQGLENG-----APCYRSRRLPGSA
	mSOCS17	---CVFHSPDITGLLEHYKDPSS-----CMFPEPLLS
	hSOCS18	---CVFHSSVTGLLEHYKDPSS-----CMFPEPLLT
	hSOCS19	EDRCQSVVEPIKRAIMHSKNGK-----FLYFLRSRVPGLP
25		* . * . *
	mCIS	VLPIPVATAVHLKLVQPFVRRSS---ARSLQHLCRLVNRLLVA---DVD
	hSOCS1	-----APLQRKR-----VRPLQELCRQRIVATVG-RENLA
	mSOCS1	-----APLQRKR-----VRPLQELCRQRIVAAVG-RENLA
30	hSOCS2	-----TVHLYLTKEPLVTSAPSLSQHLCRLTINKCTG---AIW
	hSOCS3	SPPRRAYIYSGGEKIPLVLSRPLSSNNVATLQHLCRKTVNGHLDSYEKVT
	mSOCS3	STPKRAYIYSGGEKIPLVLSRPLSSNNVATLQHLCRKTVNGHLDSYEKVT
	hSOCS14	TYP-----VRLTNFVSRFMQVRSLQYIICRFTVQYTR-IDLIQ
	mSOCS17	-----TFLIRTFP-----FSLQHICRFTVICNCIT-YDGID
35	hSOCS18	-----ISLNRTFP-----FSLQYIICRAVICRCIT-YDGID
	hSOCS19	PTP-----VQLYPVSRFSNVKSLQHLCRFRIRQLVR-IDHIP
		* . * . *
40	mCIS	CLPLPRRMADYLQYPFQL
	hSOCS1	RIPLNPVLRDYLSSFPFQI
	mSOCS1	RIPLNPVLRDYLSSFPFQI
	hSOCS2	GLPLPTRLKDYLEEYKFQV
	hSOCS3	QLPG-P-IREFLDQYDAPL
	mSOCS3	QLPG-P-IREFLDQYDAPL
45	hSOCS14	KLPLPNKMKDYLQEKHY
	mSOCS17	ALPIPSPMKLYLKEYHYKSKVRLRIRDVPEQQ
	hSOCS18	GLPLPSMLQDFLKEYHYKQKVVRVRLEREPVKAK
	hSOCS19	DLPLPKPLISYIRKFFYYQPQEEVYLSLKEAQLISKQKQEVEPST
		* . .

Table 2: Comparison of the WDS family members; WDS11 (SOCS15) and WDS12.

5	WDS12- WDS11(socs15)	MLNIIILIKFSSFSIRCAILSSVCLNEAITFAFLLQVFLWNMDKYTMIRKL MLCSAAG-----EKSVFLWMSRMSYTLIRKL .*.*****.*****.*****.*****.*****.*****.*****.*****
10	WDS12- WDS11(socs15)	EGHHHDVVACDFSPDGALLATASYDTRVYIWDPHNGDILMEFGHLFPPPT EGHQSSVSCDFSPDSALVLTASYDTSVIMWDPYIGERLRLSHHTQLEPT ***.***.*****.*****.*****.*****.*****.*****.*****.*****
15	WDS12- WDS11(socs15)	PIFAGGANDRWRVRSVFSFHDLHVASLADDKMRFWRIDEDEDYPVQVAPLS MDDSD-VHMSSLRSVCFSPEGLYLATVADDRLRRIWALELKAPVAFAPMT .*.*****.*****.*****.*****.*****.*****.*****.*****.*****
20	WDS12- WDS11(socs15)	NGLCCAFSTDGSVLAAGTHDGSVYFWATPRQVPSLQHLCRMSIRRVMPTQ NGLCCTFFPHG-GIATGTRDGHVQFWTAPPRVLSSLKHLCRKALRSFLTTY *****.*****.*****.*****.*****.*****.*****.*****.*****.*****
25	WDS12- WDS11(socs15)	EVQELPIPSKLLLEFLSYRI 219 QVLALIPKMKMKEFLTYRTF 193 .*****.*****.*****.*****.*****.*****.*****.*****.*****

All references cited herein are incorporated herein
25 by reference to the same extent as if each individual
publication or patent application was specifically and
individually indicated to be incorporated by reference in
its entirety for all purposes.

Many modifications and variations of this invention
30 can be made without departing from its spirit and scope,
as will be apparent to those skilled in the art. The
specific embodiments described herein are offered by way
of example only, and the invention is to be limited only
by the terms of the appended claims, along with the full
35 scope of equivalents to which such claims are entitled.

WHAT IS CLAIMED IS:

1. An isolated or recombinant polypeptide comprising:
 - 5 a) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 2 or 6;
 - b) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 4 or 8;
 - c) at least 17 contiguous amino acids from the
 - 10 coding portion of SEQ ID NO: 10;
 - d) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 12;
 - e) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 14; or
 - 15 f) at least 17 contiguous amino acids from the coding portion of SEQ ID NO: 16.
2. The polypeptide of claim 1, comprising the amino acid sequence of:
 - 20 a) a SOCS14 of SEQ ID NO: 2 or 6;
 - b) a SOCS15 (WDS11) of SEQ ID NO: 4 or 8;
 - c) a SOCS17 of SEQ ID NO: 10;
 - d) a SOCS18 of SEQ ID NO: 12;
 - 25 e) a SOCS19 of SEQ ID NO: 14; or
 - f) a WDS12 of SEQ ID NO: 16.
3. A fusion protein comprising the polypeptide of claim 1 or 2.
4. A binding compound which specifically binds to the polypeptide of claim 1 or 2.
- 35 5. The binding compound of claim 4 which is an antibody or antibody fragment.
6. A nucleic acid encoding the polypeptide of claim 1 or 2.
- 40 7. An expression vector comprising the nucleic acid of claim 6.
8. A host cell comprising the vector of claim 7.
- 45 9. A process for recombinantly producing a polypeptide comprising culturing the host cell of claim 8 under conditions in which the polypeptide is expressed.

SEQUENCE LISTING

SEQ ID NO: 1 is primate SOCS14 nucleic acid sequence.
SEQ ID NO: 2 is primate SOCS14 amino acid sequence.
5 SEQ ID NO: 3 is rodent SOCS15 (WDS11) nucleic acid sequence.
SEQ ID NO: 4 is rodent SOCS15 (WDS11) amino acid sequence.
SEQ ID NO: 5 is primate SOCS14 nucleic acid sequence.
SEQ ID NO: 6 is primate SOCS14 nucleic acid sequence.
SEQ ID NO: 7 is primate SOCS15 (WDS11) amino acid sequence.
10 SEQ ID NO: 8 is primate SOCS15 (WDS11) nucleic acid sequence.
SEQ ID NO: 9 is rodent SOCS17 amino acid sequence.
SEQ ID NO: 10 is rodent SOCS17 nucleic acid sequence.
SEQ ID NO: 11 is primate SOCS18 amino acid sequence.
SEQ ID NO: 12 is primate SOCS18 nucleic acid sequence.
15 SEQ ID NO: 13 is primate SOCS19 nucleic acid sequence.
SEQ ID NO: 14 is primate SOCS19 amino acid sequence.
SEQ ID NO: 15 is primate WDS12 nucleic acid sequence.
SEQ ID NO: 16 is mouse WDS12 amino acid sequence.
SEQ ID NO: 17 is mouse CIS amino acid sequence.
20 SEQ ID NO: 18 is primate SOCS1 amino acid sequence.
SEQ ID NO: 19 is murine SOCS1 amino acid sequence.
SEQ ID NO: 20 is primate SOCS2 amino acid sequence.
SEQ ID NO: 21 is primate SOCS3 amino acid sequence.
SEQ ID NO: 22 is murine SOCS3 amino acid sequence.
25 SEQ ID NO: 23 is primate SOCS16 amino acid sequence.
SEQ ID NO: 24 is primate SOCS14 nucleotide sequence.
SEQ ID NO: 25 is primate SOCS15 (WDS11) nucleotide sequence.
SEQ ID NO: 26 is rodent SOCS17 nucleotide sequence.
SEQ ID NO: 27 is primate SOCS18 nucleotide sequence.
30 SEQ ID NO: 28 is primate SOCS19 nucleotide sequence.
SEQ ID NO: 29 is primate WDS12 nucleotide sequence.

(1) GENERAL INFORMATION:

35 (i) APPLICANT:
(A) NAME: Schering Corporation
(B) STREET: 2000 Galloping Hill Road
(C) CITY: Kenilworth
40 (D) STATE: New Jersey
(E) COUNTRY: USA
(F) POSTAL CODE: 07033-0530

(ii) TITLE OF INVENTION: Suppressors of Cytokine Signaling;
45 Related Reagents

(iii) NUMBER OF SEQUENCES: 29

50 (iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette
(B) COMPUTER: Apple Macintosh
(C) OPERATING SYSTEM: Macintosh 8.0.1
(D) SOFTWARE: Microsoft Word 6.0

55 (v) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: US
(B) FILING DATE: 17-JUL-1998
(C) CLASSIFICATION:

(vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/055,804
 (B) FILING DATE: 15-AUG-1997

5 (vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/055,853
 (B) FILING DATE: 15-AUG-1997

10 (vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/053,153
 (B) FILING DATE: 18-JUL-1997

15 (vi) PRIOR APPLICATION DATA:
 (A) APPLICATION NUMBER: US 60/053,244
 (B) FILING DATE: 18-JUL-1997

(2) INFORMATION FOR SEQ ID NO:1:

20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 930 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

25 (ii) MOLECULE TYPE: cDNA

30 (ix) FEATURE:
 (A) NAME/KEY: unsure
 (B) LOCATION: 824
 (D) OTHER INFORMATION: /note= "position 824 is ambiguous;
 may be A, C, G, or T; all code for proline"

35 (ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION: 3..929

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AC GAC CTC CAG TCT GAG ACC ACG TCG CAG GAG CAA GCC AAT TCA CTG	47
Asp Leu Gln Ser Glu Thr Thr Cys Gln Gln Ala Asn Ser Leu	15
1 5 10 15	
AAG AGC TCG GCT TCT CAT AAT GGA GAC CTG CAT CTT CAC CTG GAT GAA	95
Lys Ser Ser Ala Ser His Asn Gly Asp Leu His Leu His Asp Glu	20 25 30
20 25 30	
CAT GTG CCT GTC GTT ATT GGA CTT ATG CCT CAG GAC TAC ATT CAG TAT	143
His Val Pro Val Val Ile Gly Leu Met Pro Gln Asp Tyr Ile Gln Tyr	35 40 45
35 40 45	
ACT GTG CCT TTA GAT GAG GGG ATG TAT CCT TTG GAA GGA TCA CGG AGC	191
Thr Val Pro Leu Asp Glu Gly Met Tyr Pro Leu Glu Gly Ser Arg Ser	50 55 60
50 55 60	
TAT TGT CTG GAC AGC TCT TCT CCC ATG GAA GTC TCT GCG GTT CCT CCT	239
Tyr Cys Leu Asp Ser Ser Pro Met Glu Val Ser Ala Val Pro Pro	65 70 75
65 70 75	
CAA GTG GGA GGG CGC GCT TTC CCC GAG GAT GAG AGT CAG GTA GAC CAG	287
Gln Val Gly Gly Arg Ala Phe Pro Glu Asp Glu Ser Gln Val Asp Gln	

	80	85	90	95	
5	GAC CTA GTT GTC GCC CCA GAG ATC TTC GTG GAT CAG TCC GGT GAA TGG Asp Leu Val Val Ala Pro Glu Ile Phe Val Asp Gln Ser Gly Glu Trp 100 105 110				335
	CTT GTT GAT TGG CAC CAC GGG AGT CAT GTT GCA GAA CCC CGG AGA GCG Leu Val Asp Trp His His Gly Ser His Val Ala Glu Pro Arg Arg Ala 115 120 125				383
10	GGT TCA CGA TGG ATG TCC CTC CAA TCT TCA CCA TTG GTT ACC TCC AAT Gly Ser Arg Trp Met Ser Leu Gln Ser Ser Pro Leu Val Thr Ser Asn 130 135 140				431
15	GCA GGA ATA ATC CAA ATC CCA AAG GGG ACC TTC AGT GGA CTC ACT CGG Ala Gly Ile Ile Gln Ile Pro Lys Gly Thr Phe Ser Gly Leu Thr Gly 145 150 155				479
20	ACA GAA GCC CAC GTG GCT GAA AGT ATG CGC TGT CAT TTG AAT TTT GAT Thr Glu Ala His Val Ala Glu Ser Met Arg Cys His Leu Asn Phe Asp 160 165 170 175				527
25	CCG AAC TCT CCT GGG GTT GCA AGA GTT TAT GAC TCA GTG CAA AGT Pro Asn Ser Ala Pro Gly Val Ala Arg Val Tyr Asp Ser Val Gln Ser 180 185 190				575
	AGT GGT CCC ATG GTG ACA AGC CTT ACA GAG GAG CTG AAA AAA CTT Ser Gly Pro Met Val Val Thr Ser Leu Thr Glu Glu Leu Lys Lys Leu 195 200 205				623
30	GCA AAG CAA GGA TGG TAC TGG GGA CCA ATC ACA CGT TGG GAG GCA GAA Ala Lys Gln Gly Trp Tyr Trp Gly Pro Ile Thr Arg Trp Glu Ala Glu 210 215 220				671
35	GGG AAG CTA GCA AAC GTG CCA GAT GGT TCT TTT CTT GTT CGG GAC AGT Gly Lys Leu Ala Asn Val Pro Asp Gly Ser Phe Leu Val Arg Asp Ser 225 230 235				719
40	TCT GAC GAC CGT TAC CTT TTA AGC TTG AGC TTT CGC TCC CAT GGT AAA Ser Asp Asp Arg Tyr Leu Leu Ser Leu Ser Phe Arg Ser His Gly Lys 240 245 250 255				767
45	ACA CTT CAC ACT AGA ATT GAG CAC TCA AAT GGT AGG TTT AGC TTT TAT Thr Leu His Thr Arg Ile Glu His Ser Asn Gly Arg Phe Ser Phe Tyr 260 265 270				815
	GAA CAG CCC GAT GTG GAA GGA CAT ACG TCC ATA GTT GAT CTA ATT GGA Glu Gln Pro Asp Val Glu Gly His Thr Ser Ile Val Asp Leu Ile Gly 275 280 285				863
50	GCA TTC AAT CAG GGA CTC TGA AAA TGG GAG CTT TTT GTT ATT CAA GGT Ala Phe Asn Gln Gly Leu * Lys Trp Glu Leu Phe Val Ile Gln Gly 290 295 300				911
55	CTC GGC TGC CTG GAA TCT G Leu Gly Cys Leu Glu Ser 305				930

60 (2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 309 amino acids
 (B) TYPE: amino acid

(B) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

305

(2) INFORMATION FOR SEQ ID NO:3:

5	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 476 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
10	(ii) MOLECULE TYPE: cDNA	
15	(ix) FEATURE:	
	(A) NAME/KEY: CDS	
	(B) LOCATION: 3..476	
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:	
25	CA GCT TCG TAT GAC ACC AGT GTG ATT ATG TGG GAC CCC TAC ACC GGC Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly 1 5 10 15	47
30	GAG AGG CTG AGG TCA CTT CAT CAC ACA CAG CTT GAA CCC ACC ATG GAT Glu Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp 20 25 30	95
35	GAC AGT GAC GTC CAC ATG AGC TCC CTG AGG TCC GTG TGC TTC TCA CCT Asp Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro 35 40 45	143
40	GAA GGC TTG TAT CTC GCT ACG GTG GCA GAT GAC AGG CTG CTC AGG ATC Glu Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile 50 55 60	191
45	TGG GCT CTG GAA CTG AAG GCT CCG GTT GCC TTT GCT CCG ATG ACC AAT Trp Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asn 65 70 75	239
50	GGT CTT TGC TGC ACG TTC TTC CCA CAC GGT GGA ATT ATT GCC ACA GGG Gly Leu Cys Cys Thr Phe Pro His Gly Gly Ile Ile Ala Thr Gly 80 85 90 95	287
55	ACG AGA GAT GGC CAT GTC CAG TTC TGG ACA GCT CCC CGG GTC CTG TCC Thr Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser 100 105 110	335
60	TCA CTG AAG CAC TTA TGC AGG AAA GCC CTC CGA AGT TTC CTG ACA ACG Ser Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr 115 120 125	383
65	TAT CAA GTC CTA GCA CTG CCA ATC CCC AAG AAG ATG AAA GAG TTC CTC Tyr Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu 130 135 140	431
70	ACA TAC AGG ACT TTC TAG CAG TGC CGG CTC CCC CAC CTC CTG CAG Thr Tyr Arg Thr Phe * Gln Cys Arg Leu Pro His Leu Gln 145 150 155	476

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 158 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

10 Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly Glu
1 5 10 15

Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp Asp
20 25 30

15 Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro Glu
35 40 45

Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile Trp
50 55 60

20 Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asn Gly
65 70 75 80

25 Leu Cys Cys Thr Phe Phe Pro His Gly Gly Ile Ile Ala Thr Gly Thr
85 90 95

Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser Ser
100 105 110

30 Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr Tyr
115 120 125

Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu Thr
130 135 140

35 Tyr Arg Thr Phe * Gln Cys Arg Leu Pro His Leu Leu Gln
145 150 155

(2) INFORMATION FOR SEQ ID NO:5:

40 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2093 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

45 (ii) MOLECULE TYPE: cDNA

50 (ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 87..1241

55 (ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 20
- (D) OTHER INFORMATION: /note= "nucleotide may be A or C at positions: 20, 36, 1583, 1675, 1689, 1693, 1710, 1711, 1719, 1720, 1728, 1753, 1787, and 1806."

60 (ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 35
- (D) OTHER INFORMATION: /note= "nucleotide may be G or T at

positions: 35, 1541, 1594, 1689, 1778, 1779, 1825, 1844, 1845, 1853, 1854, 1865, 1884, and 1893. "

5 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 70
(D) OTHER INFORMATION: /note= "Nucleotide may be A or G at positions: 70, 1461, 1630, 1677, 1713, 1725, 1734, 1735, 1757, 1805, 1810, and 1863. "

10 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 64
(D) OTHER INFORMATION: /note= "Nucleotide may be A or T at positions: 64, 1692, 1715, 1718, 1721, 1722, 1799, 1837, 1841, 1876, and 1894. "

15 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1661
(D) OTHER INFORMATION: /note= "Nucleotide may be C or T at positions: 1661, 1729, 1749, 1750, 1754, 1776, 1802, 1826, 1847, 1859, 1860, 1904, 1907, and 1911. "

20 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1731
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at positions: 1731, 1817, 1887, and 1908. "

25 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1869
(D) OTHER INFORMATION: /note= "Nucleotide may be C, G, or T at positions: 1869, 1883, 1885, 1886, and 1895. "

30 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1888
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, or G at positions: 1888, and 1896. "

35 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1888
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, or T at positions: 1877, and 1898. "

40 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1855
(D) OTHER INFORMATION: /note= "Nucleotide may be A, G, or T at position 1855. "

45 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1935
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, G, or T at positions: 1935, and 2034. "

50 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TAAGGTCCAC GTCGCTCCGC AGCCATCACT ACAGGCCCGC GCCGTGGCCT CTGCGGCCA

	CAATCTCCGA GGAGACCTGC ATCAAG ATG GAG GTG AGA GTC AAG GCC TTG GTT Met Glu Val Arg Val Lys Ala Leu Val 1 5	113
5	CAC TCT TCC AGC CCG AGT CCA GCC CTG AAT GGC GTC CGG AAG GAT TTC His Ser Ser Ser Pro Ser Pro Ala Leu Asn Gly Val Arg Lys Asp Phe 10 15 20 25	161
10	CAC GAC CTC CAG TCT GAG ACC ACG TGC CAG GAG CAA GCC AAT TCA CTG His Asp Leu Gln Ser Glu Thr Thr Cys Gln Glu Gln Ala Asn Ser Leu 30 35 40	209
15	AAG AGC TCG GCT TCT CAT AAT GGA GAC CTG CAT CTT CAC CTG GAT GAA Lys Ser Ser Ala Ser His Asn Gly Asp Leu His Leu His Leu Asp Glu 45 50 55	257
20	CAT GTG CCT GTC GTT ATT GGA CTT ATG CCT CAG GAC TAC ATT CAG TAT His Val Pro Val Val Ile Gly Leu Met Pro Gln Asp Tyr Ile Gln Tyr 60 65 70	305
	ACT GTG CCT TTA GAT GAG GGG ATG TAT CCT TTG GAA GGA TCA CGG AGC Thr Val Pro Leu Asp Glu Gly Met Tyr Pro Leu Glu Gly Ser Arg Ser 75 80 85	353
25	TAT TGT CTG GAC AGC TCT TCT CCC ATG GAA GTC TCT GCG GTT CCT CCT Tyr Cys Leu Asp Ser Ser Pro Met Glu Val Ser Ala Val Pro Pro 90 95 100 105	401
30	CAA GTG GGA GGG CGC GCT TTC CCC GAG GAT GAG AGT CAG GTA GAC CAG Gln Val Gly Arg Ala Phe Pro Glu Asp Glu Ser Gln Val Asp Gln 110 115 120	449
35	GAC CTA GTT GTC GCC CCA GAG ATC TTC GTG GAT CAG TCC GTG ATT GGC Asp Leu Val Ala Pro Glu Ile Phe Val Asp Gln Ser Val Asn Gly 125 130 135	497
40	TTG TTG ATT GGC ACC ACG GGA GTC ATG TTG CAG AGC CCG AGA GCG GGT Leu Leu Ile Gly Thr Thr Gly Val Met Leu Gln Ser Pro Arg Ala Gly 140 145 150	545
	CAC GAT GAT GTC CCT CCA CTC TCA CCA TTG CTA CCT CCA ATG CAG AAT His Asp Asp Val Pro Pro Leu Ser Pro Leu Leu Pro Pro Met Gln Asn 155 160 165	593
45	AAT CAA ATC CAA AGG AAC TTC ACT GGA CTC ACT GGC ACA GAA GCC CAC Asn Gln Ile Gln Arg Asn Phe Ser Gly Leu Thr Gly Thr Glu Ala His 170 175 180 185	641
50	GTC GCT GAA AGT ATG CGC TGT CAT TTG AAT TTT GAT CCG AAC TCT GCT Val Ala Glu Ser Met Arg Cys His Leu Asp Phe Asp Pro Asn Ser Ala 190 195 200	689
55	CCT GGG GTT GCA AGA GTT TAT GAC TCA GTG CAA AGT AGT GGT CCC ATG Pro Gly Val Ala Arg Val Tyr Asp Ser Val Gln Ser Ser Gly Pro Met 205 210 215	737
	GTT GTG ACA AGC CTT ACA GAG GAG CTG AAA AAA CTT GCA AAG CAA GGA Val Val Thr Ser Leu Thr Glu Glu Leu Lys Leu Ala Lys Gln Gly 220 225 230	785
60	TGG TAC TGG GGA CCA ATC ACA CGT TGG GAG GCA GAA GGG AAG CTA GCA Trp Tyr Trp Gly Pro Ile Thr Arg Trp Glu Ala Glu Gly Lys Leu Ala 235 240 245	833

	AAC GTG CCA GAT GGT TCT TTT CTT GTT CGG GAC AGT TCT GAC GAC CGT	881
	Asn Val Pro Asp Gly Ser Phe Leu Val Arg Asp Ser Ser Asp Asp Arg	
	250 255 260 265	
5	TAC CTT TTA AGC TTG AGC TTT CGC TCC CAT GGT AAA ACA CTT CAC ACT	929
	Tyr Leu Leu Ser Leu Ser Phe Arg Ser His Gly Lys Thr Leu His Thr	
	270 275 280	
10	AGA ATT GAG CAC TCA AAT GGT AGG TTT AGC TTT TAT GAA CAG CCA GAT	977
	Arg Ile Glu His Ser Asn Gly Arg Phe Ser Phe Tyr Glu Gln Pro Asp	
	285 290 295	
15	GTG GAA AGG ACA TAC TCC ATA GTT GAT CTA ATT GAG CAT TCC ATC CAG	1025
	Val Glu Arg Thr Tyr Ser Ile Val Asp Leu Ile Glu His Ser Ile Gln	
	300 305 310	
20	GGA CTC GAA AAT GGA GCT TTT TGT TAT TCA AGG TCT CGG CTG CCT GGA	1073
	Gly Leu Glu Asn Gly Ala Phe Cys Tyr Ser Arg Ser Arg Leu Pro Gly	
	315 320 325	
25	TCT GCA ACT TAC CCC GTC AGA CTG ACC AAC CCA GTG TCC CGG TTC ATG	1121
	Ser Ala Thr Tyr Pro Val Arg Leu Thr Asn Pro Val Ser Arg Phe Met	
	330 335 340 345	
	CAG GTG CGC TCG TTG CAG TAC CTG TGT CGT TTT GTT ATA CGT CAG TAT	1169
	Gln Val Arg Ser Leu Gln Tyr Leu Cys Arg Phe Val Ile Arg Gln Tyr	
	350 355 360	
30	ACC AGA ATA GAC TTA ATT CAG AAA CTG CCT TTG CCA AAC AAA ATG AAG	1217
	Thr Arg Ile Asp Leu Ile Gln Lys Leu Pro Leu Pro Asn Lys Met Lys	
	365 370 375	
35	GAT TAT TTA CAG GAG AAG CAC TAC TGAAAGATTG AGAACCCCTGC ATCTTGACT	1271
	Asp Tyr Leu Gln Glu Lys His Tyr	
	380 385	
40	TTGGGAATAA GAACAAGAGA TTGAAATACA GTTACAAAC TTTCATTGCC ATCAAAATCT	1331
	TTTGCTGCCA TAATCATTTTC AGTTTTATGT GTAAAAGAGT CATCAGTTG TTTAGGGTGT	1391
	GGGAAGTGTGTC AGCAAGGTGT CTGGGTTTA TTTGGTTCT TTAAAAAAGG GAAGTCCTGA	1451
	AGTTTTAGAA GTGTTGAATT ATGTTTCATC AATGTGCAGA ATAATCACAA TGTGAATTAT	1511
45	CAAATTCTCC TCAATGCC CCCCAGCCAT TCCCTTGCTG CTATCCACTG TGATTTTAT	1571
	GCATTAAAAG CCCATTCTAT GTTTTTCAA CCCTAAGTAA AGTTGAATGA AACTAACAG	1631
50	AATGGAAATT GCTATTTCTT TTAAATGGC CCATTTCGA AAACAAGTGT TGAATAACCA	1691
	ACCCCTGTTG AATAAAACCC GAAATTACCA ATAACACCCG AGGTGAGTTT TTAATCTCCT	1751
	55 ACCTTGAAAA GATTATTTA GAATCGGGAA TTGACCTAAT ATTGGGTAAT TGGACCGGAG	1811
	ATCTGCACA TATCTTTAA CAAACATTAA TTGGCCTTAA TTGTTTCCA AAGGTGCGCT	1871
	TATTTCTTG GGGGGGAAA GGAGGAATTC TCCGCCCCC TCGTTTCTAT CTTCTAGTTT	1931
60	GTGCTATTTT AATAATGGC CTTACATTTA AAAATTGTA AGAAATGTAT ACCACCAATT	1991
	TAGAAATTGT TGCCCTTTCT GTAAATTAAAC TCGGGTACAA ATCCGGATATA CATGAAAACC	2051
	TATGGAACTA GAATTATTAT TAAAGAAATA TTAGATGATC AT	2093

(2) INFORMATION FOR SEQ ID NO:6:

5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 385 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Glu Val Arg Val Lys Ala Leu Val His Ser Ser Ser Pro Ser Pro
15 1 5 10 15

Ala Leu Asn Gly Val Arg Lys Asp Phe His Asp Leu Gln Ser Glu Thr
20 20 25 30

20 Thr Cys Gln Glu Gln Ala Asn Ser Leu Lys Ser Ser Ala Ser His Asn
35 35 40 45

Gly Asp Leu His Leu His Leu Asp Glu His Val Pro Val Val Ile Gly
50 55 60

25 Leu Met Pro Gln Asp Tyr Ile Gln Tyr Thr Val Pro Leu Asp Glu Gly
65 70 75 80

Met Tyr Pro Leu Glu Gly Ser Arg Ser Tyr Cys Leu Asp Ser Ser Ser
30 85 90 95

Pro Met Glu Val Ser Ala Val Pro Pro Gln Val Gly Gly Arg Ala Phe
100 105 110

35 Pro Glu Asp Glu Ser Gln Val Asp Gln Asp Leu Val Val Ala Pro Glu
115 120 125

Ile Phe Val Asp Gln Ser Val Asn Gly Leu Leu Ile Gly Thr Thr Gly
40 130 135 140

Val Met Leu Gln Ser Pro Arg Ala Gly His Asp Asp Val Pro Pro Leu
145 150 155 160

Ser Pro Leu Leu Pro Pro Met Gln Asn Asn Gln Ile Gln Arg Asn Phe
45 165 170 175

Ser Gly Leu Thr Gly Thr Glu Ala His Val Ala Glu Ser Met Arg Cys
180 185 190

50 His Leu Asn Phe Asp Pro Asn Ser Ala Pro Gly Val Ala Arg Val Tyr
195 200 205

Asp Ser Val Gln Ser Ser Gly Pro Met Val Val Thr Ser Leu Thr Glu
55 210 215 220

Glu Leu Lys Lys Leu Ala Lys Gln Gly Trp Tyr Trp Gly Pro Ile Thr
225 230 235 240

Arg Trp Glu Ala Glu Gly Lys Leu Ala Asn Val Pro Asp Gly Ser Phe
60 245 250 255

Leu Val Arg Asp Ser Ser Asp Asp Arg Tyr Leu Leu Ser Leu Ser Phe
260 265 270

Arg Ser His Gly Lys Thr Leu His Thr Arg Ile Glu His Ser Asn Gly
275 280 285

5 Arg Phe Ser Phe Tyr Glu Gln Pro Asp Val Glu Arg Thr Tyr Ser Ile
290 295 300

Val Asp Leu Ile Glu His Ser Ile Gln Gly Leu Glu Asn Gly Ala Phe
305 310 315 320

10 Cys Tyr Ser Arg Ser Arg Leu Pro Gly Ser Ala Thr Tyr Pro Val Arg
325 330 335

Leu Thr Asn Pro Val Ser Arg Phe Met Gln Val Arg Ser Leu Gln Tyr
340 345 350

15 Leu Cys Arg Phe Val Ile Arg Gln Tyr Thr Arg Ile Asp Leu Ile Gln
355 360 365

20 Lys Leu Pro Leu Pro Asn Lys Met Lys Asp Tyr Leu Gln Glu Lys His
370 375 380

Tyr
385

25 (2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 1748 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

35 (ix) FEATURE:

(A) NAME/KEY: CDS
(B) LOCATION: 1..1335

40 (ix) FEATURE:

(A) NAME/KEY: misc_feature
(B) LOCATION: 1026
(D) OTHER INFORMATION: /note= "Nucleotide may be C or T at
positions: 1026, 1032, 1041, 1452, 1510, and 1567."

45 (ix) FEATURE:

(A) NAME/KEY: misc_feature
(B) LOCATION: 945
(D) OTHER INFORMATION: /note= "Nucleotide may be A or G at
positions: 945, 1376, 1541, 1658, 1662, and 1668."

50 (ix) FEATURE:

(A) NAME/KEY: misc_feature
(B) LOCATION: 1435
(D) OTHER INFORMATION: /note= "Nucleotide may be G or T at
positions: 1435, 1481, 1518, and 1543."

55 (ix) FEATURE:

(A) NAME/KEY: misc_feature
(B) LOCATION: 1500
(D) OTHER INFORMATION: /note= "Nucleotide may be A or C at
positions: 1500, and 1669."

60 (ix) FEATURE:

(A) NAME/KEY: misc_feature
(B) LOCATION: 1500
(D) OTHER INFORMATION: /note= "Nucleotide may be A or C at
positions: 1500, and 1669."

(ix) FEATURE:

(A) NAME/KEY: misc_feature
 (B) LOCATION: 1521
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or T at
 positions: 1521, and 1542."

5 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1651
 (D) OTHER INFORMATION: /note= "Nucleotide may be A, C, or
 T at position 1651."

10 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1654
 (D) OTHER INFORMATION: /note= "Nucleotide may be G, T, or
 C at position 1654."

15 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1656
 (D) OTHER INFORMATION: /note= "Nucleotide may be G, C, or
 A at position 1656."

20 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1656
 (D) OTHER INFORMATION: /note= "Nucleotide may be G, C, or
 A at position 1656."

25 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 1589..1649
 (D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T,
 or G at positions: 1589-1649, 1652, 1655, 1657-1661, 1664-1667,
 and 1672-1748."

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

ATG GAG GCC GGA GAG GAA CCG CTG CTG CTG GAA CTC AAG CCC GGG 35 Met Glu Ala Gly Glu Glu Pro Leu Leu Leu Ala Glu Leu Lys Pro Gly 1 5 10 15	48
CGC CCC CAC CAG TTT GAT TGG AAG TCC AGC TGT GAA ACC TGG AGC GTG 40 Arg Pro His Gln Phe Asp Trp Lys Ser Ser Cys Glu Thr Trp Ser Val 20 25 30	96
GCC TTC TCG CCA GAC GGT TCC TGG TTC GCC TGG TCT CAA GGA CAC TGC 45 Ala Phe Ser Pro Asp Gly Ser Trp Phe Ala Trp Ser Gln Gly His Cys 35 40 45	144
GTG GTC AAG CTG GTC CCC TGG CCC TTA GAG GAA CAG TTC ATC CCT AAA 50 Val Val Lys Leu Val Pro Trp Pro Leu Glu Glu Gln Phe Ile Pro Lys	192
55 GGA TTC GAA GCC AAG AGC CGA AGC AGC AAG AAT GAC CCA AAA GGA CGG Gly Phe Glu Ala Lys Ser Arg Ser Ser Lys Asn Asp Pro Lys Gly Arg 65 70 75 80	240
GGC AGT CTG AAG GAG AAG ACG CTG GAC TGT GGC CAG ATT GTG TGG GGG 55 Gly Ser Leu Lys Glu Lys Thr Leu Asp Cys Gly Gln Ile Val Trp Gly 85 90 95	288
CTG GCC TTC AGC CCA TGG CCC TCT CCA CCC AGC AGG AAA CTC TGG GCA 60 Leu Ala Phe Ser Pro Trp Pro Ser Pro Pro Ser Arg Lys Leu Trp Ala 100 105 110	336
CGT CAC CAT CCC CAG GCG CCT GAT GTT TCT TGC CTG ATC CTC TGG GCA 65 Arg His His Pro Gln Ala Pro Asp Val Ser Cys Leu Ile Leu Ala Thr 115 120 125	384

	GGT CTC AAC GAT GGG CAG ATC AAG ATT TGG GAG GTA CAG ACA GGC CTC Gly Leu Asn Asp Gly Gln Ile Lys Ile Trp Glu Val Gln Thr Gly Leu 130 135 140	432
5	CTG CTT CTG AAT CTT TCT GGC CAC CAA GAC GTC GTG AGA GAT CTG AGC Leu Leu Leu Asn Leu Ser Gly His Gln Asp Val Val Arg Asp Leu Ser 145 150 155 160	480
10	TTC ACG CCC AGC GGC AGT TTG ATT TTG GTC TCT GCA TCC CGG GAT AAG Phe Thr Pro Ser Gly Ser Leu Ile Leu Val Ser Ala Ser Arg Asp Lys 165 170 175	528
15	ACA CTT CGA ATT TGG GAC CTG CTC AAT AAG CAC GGT AAG CAG ATC CAG GTG Thr Leu Arg Ile Trp Asp Leu Asn Lys His Gly Lys Gln Ile Gln Val 180 185 190	576
20	TTA TCC GGC CAT CTG CAG TGG GTT TAC TGC TGC TCC ATC TCC CCT GAC Leu Ser Gly His Leu Gln Trp Val Tyr Cys Cys Ser Ile Ser Pro Asp 195 200 205	624
25	TGT AGC ATG CTG TGC TCT GCA GCT GGG GAG AAG TCG GTC TTT CTG TGG Cys Ser Met Leu Cys Ser Ala Ala Gly Lys Ser Val Phe Leu Trp 210 215 220	672
30	AGC ATG CGG TCC TAC ACA CTA ATC CGG AAA CTA GAA GGC CAC CAA AGC Ser Met Arg Ser Tyr Thr Leu Ile Arg Lys Leu Glu Gly His Gln Ser 225 230 235 240	720
35	AGT GTT GTC TCC TGT GAT TTC TCT CCT GAT TCA GCC TTG CTT GTC ACA Ser Val Val Ser Cys Asp Phe Ser Pro Asp Ser Ala Leu Leu Val Thr 245 250 255	768
40	GCT TCG TAT GAC ACC AGT GTG ATT ATG TGG GAC CCC TAC ACC GGC GAG Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly Glu 260 265 270	816
45	AGG CTG AGG TCA CTT CAT CAC ACA CAG CTT GAA CCC ACC ATG GAT GAC Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp Asp 275 280 285	864
50	AGT GAC GTC CAC ATG AGC TCC CTG AGG TCC GTG TGC TTC TCA CCT GAA Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro Glu 290 295 300	912
55	GGC TTG TAT CTC GCT ACG GTG GCA GAT GAC AGA CTG CTC AGG ATC TGG Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile Trp 305 310 315 320	960
60	GCT CTG GAA CTG AAA GCT CCG GTT GCC TTT GCT CCG ATG ACC AAT GGT Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asn Gly 325 330 335	1008
65	CTT TGC TGC ACA TTT TTC CCA CAC GGT GGA ATC ATT GCC ACA GGG ACA Leu Cys Cys Thr Phe Phe Pro His Gly Gly Ile Ile Ala Thr Gly Thr 340 345 350	1056
70	AGA GAT GGC CAC GTC CAG TTC TGG ACA GCT CCT AGG GTC CTG TCC TCA Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser Ser 355 360 365	1104
75	CTG AAG CAC TTA TGC CGG AAA GCC CTT CGA AGT TTC CTA ACA ACT TAC Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr Tyr 370 375 380	1152

CAA GTC CTA GCA CTG CCA ATC CCC AAG AAA ATG AAA GAG TTC CTC ACA	1200
Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu Thr	
385 390 395 400	
5 TAC AGG ACT TTT TAA GCA ACA CCA CAT CTT GTG CTT CTT TGT AGC AGG	1248
Tyr Arg Thr Phe * Ala Thr Pro His Leu Val Leu Leu Ser Cys Ser Arg	
405 410 415	
10 GTA AAT CGT CCT GTC AAA GGG AGT TGC TGG AAT AAT GGG CCA AAC ATC	1296
Val Asn Arg Pro Val Lys Gly Ser Cys Trp Asn Asn Gly Pro Asn Ile	
420 425 430	
15 TGG TCT TGC ATT GAA ATA GCA TTT CTT TGG GAT TGT GAA TAGAATGTA	1345
Trp Ser Cys Ile Glu Ile Ala Phe Leu Trp Asp Cys Glu	
435 440 445	
20 CAAAAACAGA TTCCAGTGTGTA CTAGTCATGG GTCTTTCTCT CCCTGGGCAT GTGGAAAGTC	1405
25 AGTCTTAGGA GGGAAAGGAGA TTCCACTTGG CACGGGCAAC AGAGCCCTTA CGTTTAAATT	1465
TTTCAGTCCA GTTATTGAAC AGCAAGTGTGTT TGAATCTTT CTGGCTTGTT TTGGATTTC	1525
25 AAGTGGCAGT TACTGGTGGT TGTTTTGGA TTTATGGCAA CCAAGTTAGG GCCCTCCAGCG	1585
GTTCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCC	1645
CCCCCTCCACC CGGCCCATCC CCACATCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCC	1705
30 CCCCCCCCCC CCCCCCCCCC CCCCCCCCCC CCCCCCCCC CCC	1748

(2) INFORMATION FOR SEQ ID NO:8:

35 (i) SEQUENCE CHARACTERISTICS:	
(A) LENGTH: 445 amino acids	
(B) TYPE: amino acid	
(D) TOPOLOGY: linear	
40 (ii) MOLECULE TYPE: protein	
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:	
45 Met Glu Ala Gly Glu Glu Pro Leu Leu Ala Glu Leu Lys Pro Gly	
1 5 10 15	
Arg Pro His Gln Phe Asp Trp Lys Ser Ser Cys Glu Thr Trp Ser Val	
20 25 30	
50 Ala Phe Ser Pro Asp Gly Ser Trp Phe Ala Trp Ser Gln Gly His Cys	
35 40 45	
55 Val Val Lys Leu Val Pro Trp Pro Leu Glu Glu Gln Phe Ile Pro Lys	
50 55 60	
55 Gly Phe Glu Ala Lys Ser Arg Ser Ser Lys Asn Asp Pro Lys Gly Arg	
65 70 75 80	
60 Gly Ser Leu Lys Glu Lys Thr Leu Asp Cys Gly Gln Ile Val Trp Gly	
85 90 95	
Leu Ala Phe Ser Pro Trp Pro Ser Pro Pro Ser Arg Lys Leu Trp Ala	
100 105 110	

	Arg His His Pro Gln Ala Pro Asp Val Ser Cys Leu Ile Leu Ala Thr			
	115	120	125	
	Gly Leu Asn Asp Gly Gln Ile Lys Ile Trp Glu Val Gln Thr Gly Leu			
5	130	135	140	
	Leu Leu Leu Asn Leu Ser Gly His Gln Asp Val Val Arg Asp Leu Ser			
	145	150	155	160
10	Phe Thr Pro Ser Gly Ser Leu Ile Leu Val Ser Ala Ser Arg Asp Lys			
	165	170	175	
	Thr Leu Arg Ile Trp Asp Leu Asn Lys His Gly Lys Gln Ile Gln Val			
	180	185	190	
15	Leu Ser Gly His Leu Gln Trp Val Tyr Cys Cys Ser Ile Ser Pro Asp			
	195	200	205	
20	Cys Ser Met Leu Cys Ser Ala Ala Gly Glu Lys Ser Val Phe Leu Trp			
	210	215	220	
	Ser Met Arg Ser Tyr Thr Leu Ile Arg Lys Leu Glu Gly His Gln Ser			
	225	230	235	240
25	Ser Val Val Ser Cys Asp Phe Ser Pro Asp Ser Ala Leu Leu Val Thr			
	245	250	255	
	Ala Ser Tyr Asp Thr Ser Val Ile Met Trp Asp Pro Tyr Thr Gly Glu			
	260	265	270	
30	Arg Leu Arg Ser Leu His His Thr Gln Leu Glu Pro Thr Met Asp Asp			
	275	280	285	
35	Ser Asp Val His Met Ser Ser Leu Arg Ser Val Cys Phe Ser Pro Glu			
	290	295	300	
	Gly Leu Tyr Leu Ala Thr Val Ala Asp Asp Arg Leu Leu Arg Ile Trp			
	305	310	315	320
40	Ala Leu Glu Leu Lys Ala Pro Val Ala Phe Ala Pro Met Thr Asn Gly			
	325	330	335	
	Leu Cys Cys Thr Phe Pro His Gly Gly Ile Ile Ala Thr Gly Thr			
	340	345	350	
45	Arg Asp Gly His Val Gln Phe Trp Thr Ala Pro Arg Val Leu Ser Ser			
	355	360	365	
	Leu Lys His Leu Cys Arg Lys Ala Leu Arg Ser Phe Leu Thr Thr Tyr			
50	370	375	380	
	Gln Val Leu Ala Leu Pro Ile Pro Lys Lys Met Lys Glu Phe Leu Thr			
	385	390	395	400
55	Tyr Arg Thr Phe * Ala Thr Pro His Leu Val Leu Leu Cys Ser Arg			
	405	410	415	
	Val Asn Arg Pro Val Lys Gly Ser Cys Trp Asn Asn Gly Pro Asn Ile			
	420	425	430	
60	Trp Ser Cys Ile Glu Ile Ala Phe Leu Trp Asp Cys Glu			
	435	440	445	

(2) INFORMATION FOR SEQ ID NO:9:

5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2198 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: cDNA

15 (ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 1..1419

20 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1680
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T,
or G at positions: 1680, 1691, 1696, 1704, 1707, 1728, 1740,
1743, 1746, 1755, 1760, 1770, 1773, 1802, 1816, 1817, 1823,
1826, 1827, 1846, 1851, 1857, 1861, 1880, and 1885."

25 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1909
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T,
or G at positions: 1909, 1917, 1920, 1929, 1946, 1953, 1967-8,
1980, 1991, 1995, 2001, 2004, 2021, 2033-37, 2039-40, 2042,
2048, 2051, 2054, 2061, 2075, 2081, and 2083-85."

30 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 2088
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T,
or G at positions: 2088, 2105, 2121, 2124, 2132, 2137, 2147,
2149, 2151-52, 2160, 2165, 2177, 2179 and 2196."

35 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 494
(D) OTHER INFORMATION: /note= "Nucleotide may be A or C at
position 494."

40 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 498
(D) OTHER INFORMATION: /note= "Nucleotide may be A or C at
position 494."

45 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 498
(D) OTHER INFORMATION: /note= "Nucleotide may be C or T at
positions: 498, 501, 1455, 1524, 1527, 1621, 1829, and 2072."

50 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 499
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at
positions: 499, 1618, and 1664."

55 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1673
(D) OTHER INFORMATION: /note= "Nucleotide may be G or T at
position 1673."

60 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1819

(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, or G at positions: 1819, 1840, and 2089."

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GGC GGT GGT GAT GGC GGC AGG CGC TCG GAC AGC TCC GCT TGA GCT GAG	48
Gly Gly Gly Asp Gly Gly Arg Arg Ser Asp Ser Ser Ala * Ala Glu	
1 5 10 15	
10 CTC GGA GAG ATC CGT CCA GAA AGT GCC CAG AAG AAA CTT CCT CTT AGA	96
Leu Gly Glu Ile Arg Pro Glu Ser Ala Gln Lys Lys Leu Pro Leu Arg	
20 25 30	
15 AAA GCT GAA AAC ACA ATA TTT ATA ACA CTG GAA ATT GTA AAG AAT TTG	144
Lys Ala Glu Asn Thr Ile Phe Ile Thr Leu Glu Ile Val Lys Asn Leu	
35 40 45	
20 TTT AAA ATG GCT GAA AAC AAT AGT AAA AAT GTA GAT GTA CGG CCT AAA	192
Phe Lys Met Ala Glu Asn Asn Ser Lys Asn Val Asp Val Arg Pro Lys	
50 55 60	
25 ACA AGT CGG AGT CGA AGT GCT GAC AGG AAG GAT GGT TAT GTG TGG AGT	240
Thr Ser Arg Ser Arg Ser Ala Asp Arg Lys Asp Gly Tyr Val Trp Ser	
65 70 75 80	
30 GGA AAG AAG TTG TCT TGG TCC AAA AAG AGT GAG AGT TGT TCT GAA TCT	288
Gly Lys Lys Leu Ser Trp Ser Lys Lys Ser Glu Ser Cys Ser Glu Ser	
85 90 95	
35 GAA GCC AAG AAA GGG CAG CTT AGC TGT TCG TCC ATT GAG TTG GAC TTA	336
Glu Ala Lys Gly Gln Leu Ser Cys Ser Ser Ile Glu Leu Asp Leu	
100 105 110	
40 GAT CAT TCC TGT GGG CAT AGA TTT TTA GGC CGA TCC CTT AAA CAG AAA	384
Asp His Ser Cys Gly His Arg Phe Leu Gly Arg Ser Leu Lys Gln Lys	
115 120 125	
45 CTG CAA GAT GCG GTG GGG CAG TGT TTT CCA ATA AAG AAT TGT AGT GGC	432
Leu Gln Asp Ala Val Gly Gln Cys Phe Pro Ile Lys Asn Cys Ser Gly	
130 135 140	
50 CGA CAC TCT CCA GGG CTT CCA TCT AAA AGA AAG ATT CAT ATC AGT GAA	480
Arg His Ser Pro Gly Leu Pro Ser Lys Arg Lys Ile His Ile Ser Glu	
145 150 155 160	
55 CTC ATG TTA GAT ACG TGC CCC TTC CCA CCT CGC TCA GAT TTA GCC TTT	528
Leu Met Leu Asp Thr Cys Pro Phe Pro Pro Arg Ser Asp Leu Ala Phe	
165 170 175	
60 AGG TGG CAT TTT ATT AAA CGA CAC ACT GTT CCT ATG AGT CCC AAC TCA	576
Arg Trp His Phe Ile Lys Arg His Thr Val Pro Met Ser Pro Asn Ser	
180 185 190 195	
55 GAT GAA TGG GTG AGT GCA GAC CTG TCT GAG AGG AAA CTG AGA GAT GCT	624
Asp Glu Trp Val Ser Ala Asp Leu Ser Glu Arg Lys Leu Arg Asp Ala	
195 200 205	
60 CAG CTG AAA CGA AGA AAC ACA GAA GAT GAC ATA CCC TGT TTC TCA CAT	672
Gln Leu Lys Arg Arg Asn Thr Glu Asp Asp Ile Pro Cys Phe Ser His	
210 215 220	
65 ACC AAT GGC CAG CCT TGT GTC ATA ACT GCC AAC AGT GCT TCG TGT ACA	720
Thr Asn Gly Gln Pro Cys Val Ile Thr Ala Asn Ser Ala Ser Cys Thr	

	225	230	235	240	
5	GGT GGT CAC ATA ACT GGT TCT ATG ATG AAC TTG GTC ACA AAC AAC AGC Gly Gly His Ile Thr Gly Ser Met Met Asn Leu Val Thr Asn Asn Ser 245 250 255				768
	ATA GAA GAC AGT GAC ATG GAT TCA GAG GAT GAA ATT ATA ACG CTG TGC Ile Glu Asp Ser Asp Met Asp Ser Glu Asp Glu Ile Ile Thr Leu Cys 260 265 270				816
10	ACA AGC TCC AGA AAA AGG AAT AAG CCC AGG TGG GAA ATG GAA GAG GAG Thr Ser Arg Lys Arg Asn Lys Pro Arg Trp Glu Met Glu Glu Glu 275 280 285				864
15	ATC CTG CAG TTG GAG GCA CCT CCT AAG TTC CAC ACC CAG ATC GAC TAC Ile Leu Gln Leu Glu Ala Pro Pro Lys Phe His Thr Gln Ile Asp Tyr 290 295 300				912
20	GTC CAC TGC CTT GTT CCA GAC CTC CTT CAG ATC AGT AAC AAT CCG TGC Val His Cys Leu Val Pro Asp Leu Leu Gln Ile Ser Asn Asn Pro Cys 305 310 315 320				960
25	TAC TGG GGT GTC ATG GAC AAA TAT GCA GCC GAA GCT CTG CTG GAA GGA Tyr Trp Gly Val Met Asp Lys Tyr Ala Ala Glu Ala Leu Glu Gly 325 330 335				1008
	AAG CCA GAG GCC ACC TTT TTA CTT CGA GAT TCA GCG CAG GAA GAT TAT Lys Pro Glu Gly Thr Phe Leu Leu Arg Asp Ser Ala Gln Glu Asp Tyr 340 345 350				1056
30	TTA TTC TCT GTT AGT TTT AGA CGC TAC AGT CGT TCT CTT CAT GCT AGA Leu Phe Ser Val Ser Phe Arg Arg Tyr Ser Arg Ser Leu His Ala Arg 355 360 365				1104
35	ATT GAG CAG TGG AAT CAT AAC TTT AGC TTT GAT GCC CAT GAT CCT TGT Ile Glu Gln Trp Asn His Asn Phe Ser Phe Asp Ala His Asp Pro Cys 370 375 380				1152
40	GTC TTC CAT TCT CCT GAT ATT ACT GGG CTC CTG GAA CAC TAT AAG GAC Val Phe His Ser Pro Asp Ile Thr Gly Leu Leu Glu His Tyr Lys Asp 385 390 395 400				1200
45	CCC AGT GCC TGT ATG TTC TTT GAG CCG CTC TTG TCC ACT CCC TTA ATC Pro Ser Ala Cys Met Phe Phe Glu Pro Leu Leu Ser Thr Pro Leu Ile 405 410 415				1248
	CGG ACG TTC CCC TTT TCC TTG CAG CAT ATT TGC AGA ACC GTT ATT TGT Arg Thr Phe Pro Phe Ser Leu Gln His Ile Cys Arg Thr Val Ile Cys 420 425 430				1296
50	AAT TGT ACG ACT TAC GAT GGC ATC GAT GCC CTT CCC ATT CCT TCG CCT Asn Cys Thr Thr Tyr Asp Gly Ile Asp Ala Leu Pro Ile Pro Ser Pro 435 440 445				1344
55	ATG AAA TTG TAT CTG AAG GAA TAC CAT TAT AAA TCA AAA GTT AGG TTA Met Lys Leu Tyr Leu Lys Glu Tyr His Tyr Lys Ser Lys Val Arg Leu 450 455 460				1392
60	CTC AGG ATT GAT GTG CCA GAG CAG CAG TGATGCGGAG AGGTTAGAAT Leu Arg Ile Asp Val Pro Glu Gln Gln 465 470				1439
	GTCCACCGGA GCTTTGTTC CCTTTAGTGA GGGTTAATTT CGAGCTTGGC GTAATCATGG				1499

TCATAGCTGT TTCCCTGTGTG	AAATTGTTAT	CCGGCTCACAA	TTCCACACAA	CATACGAGCC	1559	
GGAAGCATAA	AGTGTAAGC	CTGGGGTCC	TAATGAGTGA	GCTAACTCAC	1619	
5	TCGCCTCAC	TGCCCCCTT	CCAGTCGGGA	AACCTGCTGT	GCCAGCTGCA	1679
	CGCCAACTCG	CGGGGACAGC	GGTTAGCCTA	TTGGGCGCTC	TTCACTTCCT	1739
	CTCCCTCCCT	CGGTCTTCG	CTGCTGCTAC	CGCTCTCCCC	ATCCAAGCGT	1799
10	CCCCAGAACT	GGGAAACCCC	GAACACCCCTC	ACAAAGCTCA	CTGCTACCGT	1859
	CCGGCTTTTC	CTCGTCCCCC	CACACCTAA	ACAGCCCTCG	AGTGCAACCC	1919
15	CTCTTCCCTC	AACCCCTGCC	TCTGTCCCCG	CCTCCGACTT	CGCTTCCCCG	1979
	CCCCCGTAGT	CCGTCTTAGT	GCAGCGCGCC	TTCCACCCCT	CCACCCCTAC	2039
20	CCCCAAACCC	CCCCCCCCCTC	CCGATAAAAAA	GTCAAGCGCT	TCACCCCCC	2099
	GTCCCCCTACT	TTCCAATGTC	TCCCCCCCCG	CTCTCTCGC	CACCAAATC	2159
	CACTGCATCC	GGTGCTACCC	TCCTGTTTCT	CCTCCCCC		2198

25 (2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 473 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Gly	Gly	Gly	Asp	Gly	Gly	Arg	Arg	Ser	Asp	Ser	Ser	Ala	*	Ala	Glu	
1				5				10					15			
40	Leu	Gly	Glu	Ile	Arg	Pro	Glu	Ser	Ala	Gln	Lys	Lys	Leu	Pro	Leu	Arg
				20				25					30			
45	Lys	Ala	Glu	Asn	Thr	Ile	Phe	Ile	Thr	Leu	Glu	Ile	Val	Lys	Asn	Leu
				35				40					45			
50	Phe	Lys	Met	Ala	Glu	Asn	Asn	Ser	Lys	Asn	Val	Asp	Val	Arg	Pro	Lys
				50				55				60				
55	Thr	Ser	Arg	Ser	Arg	Ser	Ala	Asp	Arg	Lys	Asp	Gly	Tyr	Val	Trp	Ser
				65				70				75			80	
60	Gly	Lys	Lys	Leu	Ser	Trp	Ser	Lys	Lys	Ser	Glu	Ser	Cys	Ser	Glu	Ser
				85				90				95				
65	Glu	Ala	Lys	Lys	Gly	Gln	Leu	Ser	Cys	Ser	Ser	Ile	Glu	Leu	Asp	Leu
				100				105				110				
70	Asp	His	Ser	Cys	Gly	His	Arg	Phe	Leu	Gly	Arg	Ser	Leu	Lys	Gln	Lys
				115				120				125				
75	Leu	Gln	Asp	Ala	Val	Gly	Gln	Cys	Phe	Pro	Ile	Lys	Asn	Cys	Ser	Gly
				130				135				140				
80	Arg	His	Ser	Pro	Gly	Leu	Pro	Ser	Lys	Arg	Lys	Ile	His	Ile	Ser	Glu

145	150	155	160
Leu Met Leu Asp Thr Cys Pro Phe Pro Pro Arg Ser Asp Leu Ala Phe			
165 170 175			
5	Arg Trp His Phe Ile Lys Arg His Thr Val Pro Met Ser Pro Asn Ser		
	180	185	190
10	Asp Glu Trp Val Ser Ala Asp Leu Ser Glu Arg Lys Leu Arg Asp Ala		
	195	200	205
Gln Leu Lys Arg Arg Asn Thr Glu Asp Asp Ile Pro Cys Phe Ser His			
	210	215	220
15	Thr Asn Gly Gln Pro Cys Val Ile Thr Ala Asn Ser Ala Ser Cys Thr		
	225	230	235
240			
Gly Gly His Ile Thr Gly Ser Met Met Asn Leu Val Thr Asn Asn Ser			
	245	250	255
20	Ile Glu Asp Ser Asp Met Asp Ser Glu Asp Glu Ile Ile Thr Leu Cys		
	260	265	270
25	Thr Ser Ser Arg Lys Arg Asn Lys Pro Arg Trp Glu Met Glu Glu Glu		
	275	280	285
Ile Leu Gln Leu Glu Ala Pro Pro Lys Phe His Thr Gln Ile Asp Tyr			
	290	295	300
30	Val His Cys Leu Val Pro Asp Leu Leu Gln Ile Ser Asn Asn Pro Cys		
	305	310	315
320			
Tyr Trp Gly Val Met Asp Lys Tyr Ala Ala Glu Ala Leu Leu Glu Gly			
	325	330	335
35	Lys Pro Glu Gly Thr Phe Leu Leu Arg Asp Ser Ala Gln Glu Asp Tyr		
	340	345	350
Leu Phe Ser Val Ser Phe Arg Arg Tyr Ser Arg Ser Leu His Ala Arg			
40	355	360	365
Ile Glu Gln Trp Asn His Asn Phe Ser Phe Asp Ala His Asp Pro Cys			
	370	375	380
45	Val Phe His Ser Pro Asp Ile Thr Gly Leu Leu Glu His Tyr Lys Asp		
	385	390	395
400			
Pro Ser Ala Cys Met Phe Phe Glu Pro Leu Leu Ser Thr Pro Leu Ile			
	405	410	415
50	Arg Thr Phe Pro Phe Ser Leu Gln His Ile Cys Arg Thr Val Ile Cys		
	420	425	430
Asn Cys Thr Thr Tyr Asp Gly Ile Asp Ala Leu Pro Ile Pro Ser Pro			
55	435	440	445
Met Lys Leu Tyr Leu Lys Glu Tyr His Tyr Lys Ser Lys Val Arg Leu			
	450	455	460
60	Leu Arg Ile Asp Val Pro Glu Gln Gln		
	465	470	

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2254 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: cDNA

10 (ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 117..1724

15 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 740
(D) OTHER INFORMATION: /note= "Nucleotide may be A or C at positions: 740, 797, 2139, and 2184."

20 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 761
(D) OTHER INFORMATION: /note= "Nucleotide may be G or T at positions: 761, 1313, 1508, and 2226."

25 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 746
(D) OTHER INFORMATION: /note= "Nucleotide may be C or T at positions: 746, 1460, 1499, 2009, 2010, 2199, and 2225."

30 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 788
(D) OTHER INFORMATION: /note= "Nucleotide may be A or G at positions 788, 863, 1550, 2178, 2188, 2197, and 2211."

35 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 1163
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at positions: 1163, and 1544."

40 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 2058
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at positions: 2058, and 2128."

45 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 2251
(D) OTHER INFORMATION: /note= "Nucleotide may be A or T at positions 2251."

50 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 2251
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T, or G at position 2251."

55 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

60 CTCGGGCCGG GATGGATCCG CCGGAAAGAG GAAGACAAGC GGAGCGTGTGA GCCCCCTGCGC 60
60 ACGGTGCCCC CGCGCTAGTG GGAGCTTACT CGCAGTAGCT CTCGGCTTTC TAATCA 116
65 ATG GAT AAA GTG GGG AAA ATG TGG AAC AAC TTA AAA TAC AGA TGC CAG 164
65 Met Asp Lys Val Gly Lys Met Trp Asn Asn Leu Lys Tyr Arg Cys Gln

	1	5	10	15	
	AAT CTC TTC AGC CAC GAG GGA GGA AGC CGT AAT GAG AAC GTG GAG ATG				212
5	Asn Leu Phe Ser His Glu Gly Gly Ser Arg Asn Glu Asn Val Glu Met	20	25	30	
	AAC CCC AAC AGA TGT CCG TCT GTC AAA GAG AAA AGC ATC AGT CTG GGA				260
	Asn Pro Asn Arg Cys Pro Ser Val Lys Glu Lys Ser Ile Ser Leu Gly	35	40	45	
10	GAG GCA GCT CCC CAG CAA GAG AGC AGT CCC TTA AGA GAA AAT GTT GCC				308
	Glu Ala Ala Pro Gln Gln Glu Ser Ser Pro Leu Arg Glu Asn Val Ala	50	55	60	
15	TTA CAG CTG GGA CTG AGC CCT TCC AAG ACC TTT TCC AGG CGG AAC CAA				356
	Leu Gln Leu Gly Leu Ser Pro Ser Lys Thr Phe Ser Arg Arg Asn Gln	65	70	75	
20	AAC TGT GCC GCA GAG ATC CCT CAA GTG GTT GAA ATC AGC ATC GAG AAA				404
	Asn Cys Ala Ala Glu Ile Pro Gln Val Val Glu Ile Ser Ile Glu Lys	85	90	95	
25	GAC AGT GAC TCG GGT GCC ACC CCA GGA ACG AGG CTT GCA CGG AGA GAC				452
	Asp Ser Asp Ser Gly Ala Thr Pro Gly Thr Arg Leu Ala Arg Arg Asp	100	105	110	
	TCC TAC TCG CGG CAC GCC CCG TGG GGA GGA AAG AAG AAA CAT TCC TGT				500
	Ser Tyr Ser Arg His Ala Pro Trp Gly Gly Lys Lys His Ser Cys	115	120	125	
30	TCC ACA AAG ACC CAG AGT TCA TTG GAT ACC GAG AAA AAG TTT GGT AGA				548
	Ser Thr Lys Thr Gln Ser Ser Leu Asp Thr Glu Lys Phe Gly Arg	130	135	140	
35	ACT CGA AGC GGC CTT CAG AGG CGA GAG CGG CGC TAT GGA GTC AGC TCC				596
	Thr Arg Ser Gly Leu Gln Arg Arg Glu Arg Arg Tyr Gly Val Ser Ser	145	150	155	
40	ATG CAG GAC ATG GAC AGC GTT TCT AGC CGC GCG GTC GGG AGC CGC TCC				644
	Met Gln Asp Met Asp Ser Val Ser Arg Ala Val Gly Ser Arg Ser	165	170	175	
45	CTG AGG CAG AGG CTC CAG GAC AGC GTG GGT TTG TGT TTT CCC ATG AGA				692
	Leu Arg Gln Arg Leu Gln Asp Thr Val Gly Leu Cys Phe Pro Met Arg	180	185	190	
	ACT TAC AGC AAG CAG TCA AAG CCA CTC TTT TCC AAT AAA AGA AAA ATC				740
	Thr Tyr Ser Lys Gln Ser Lys Pro Leu Phe Ser Asn Lys Arg Lys Ile	195	200	205	
50	CAT CTC TCT GAA TTA ATG CTG GAG AAA TGC CCT TTT CCT GCT GGC TCG				788
	His Leu Ser Glu Leu Met Leu Glu Lys Cys Pro Phe Pro Ala Gly Ser	210	215	220	
55	GAT TTA GCC CAA AAG TGG CAT TTG ATT AAA CAG CAT ACA GCT CCT GTG				836
	Asp Leu Ala Gln Lys Trp His Leu Ile Lys Gln His Thr Ala Pro Val	225	230	235	
60	AGC CCA CAT TCA ACA TTT TTT GAT ACG TTT GAT CCA TCT TTG GTT TCT				884
	Ser Pro His Ser Thr Phe Phe Asp Thr Phe Asp Pro Ser Leu Val Ser	245	250	255	
	ACA GAA GAT GAA GAA GAT AGG CTT AGA GAG AGA AGG CGG CTT AGT ATT				932
	Thr Glu Asp Glu Glu Asp Arg Leu Arg Glu Arg Arg Leu Ser Ile				

	260	265	270	
5	GAA GAA GGG GTT GAT CCC CCT CCC AAT GCA CAA ATA CAT ACA TTT GAA Glu Glu Gly Val Asp Pro Pro Pro Asn Ala Gln Ile His Thr Phe Glu 275 280 285			980
10	GCT ACT GCA CAG GTT AAT CCA TTA TTT AAA CTG GGA CCA AAA TTA GCT Ala Thr Ala Gln Val Asn Pro Leu Phe Lys Leu Gly Pro Lys Leu Ala 290 295 300			1028
15	CCT GGA ATG ACT GAA ATA AGT GGG GAC AGT TCT GCA ATT CCA CAA GCT Pro Gly Met Thr Glu Ile Ser Gly Asp Ser Ala Ile Pro Gln Ala 305 310 315 320			1076
20	AAT TGT GAC TCG GAA GAG GAT ACA ACC ACC CTG TGT TTG CAG TCA CGG Asn Cys Asp Ser Glu Glu Asp Thr Thr Leu Cys Leu Gln Ser Arg 325 330 335			1124
25	AGG CAG AAG CAG CGT CAG ATA TCT GGA GAC AGC CAT ACC CAT GTT AGC Arg Gln Lys Gln Arg Gln Ile Ser Gly Asp Ser His Thr His Val Ser 340 345 350			1172
30	AGA CAG GGA GCT TGG AAA GTC CAC ACA CAG ATT GAT TAC ATA CAC TGC Arg Gln Gly Ala Trp Lys Val His Thr Gln Ile Asp Tyr Ile His Cys 355 360 365			1220
35	CTC GTG CCT GAT TTG CTT CAA ATT ACA GGG AAT CCC TGT TAC TGG GGA Leu Val Pro Asp Leu Leu Gln Ile Thr Gly Asn Pro Cys Tyr Trp Gly 370 375 380			1268
40	GTG ATG GAC CGT TAT GAA GCA GAA GCC CTC TCC GAA GGG AAA CCG GAA Val Met Asp Arg Tyr Glu Ala Glu Ala Leu Ser Glu Gly Lys Pro Glu 385 390 395 400			1316
45	GGC ACG TTC TTG CTC AGG GAC TCT GCA CAG GAG GAC TAC CTC TTC TCT Gly Thr Phe Leu Leu Arg Asp Ser Ala Gln Glu Asp Tyr Leu Phe Ser 405 410 415			1364
50	GTG AGT TCC GCC GCT ACA ACA GGA TCT CTG CAC GCC CGG ATC GAG CAG Val Ser Ser Ala Ala Thr Thr Gly Ser Leu His Ala Arg Ile Glu Gln 420 425 430			1412
55	TGG AAC CAC AAC TTC AGC TTC GAT GCC CAT GAC CCC TGC GTG TTT CAC Trp Asn His Asn Phe Ser Phe Asp Ala His Asp Pro Cys Val Phe His 435 440 445			1460
60	TCC TCC ACT GTC ACG GGG CTT CTC GAA CAC TAT AAA GAC CCC AGT TCG Ser Ser Thr Val Thr Gly Leu Leu Glu His Tyr Lys Asp Pro Ser Ser 450 455 460			1508
65	TGC ATG TTT TTT GAA CCG TTG CTA ACG ATA TCA CTC AAT AGG ACT TTC Cys Met Phe Glu Pro Leu Leu Thr Ile Ser Leu Asn Arg Thr Phe 465 470 475 480			1556
70	CCT TTC AGC CTG CAG TAT ATC TGC CGC GCA GTG ATC TGC AGA TGC ACT Pro Phe Ser Leu Gln Tyr Ile Cys Arg Ala Val Ile Cys Arg Cys Thr 485 490 495			1604
75	ACG TAT GAT GGG ATT GAC GGG CTC CCG CTA CCG TCG ATG TTA CAG GAT Thr Tyr Asp Gly Ile Asp Gly Leu Pro Leu Pro Ser Met Leu Gln Asp 500 505 510			1652
80	TTT TTA AAA GAG TAT CAT TAT AAA CAA AAA GTT AGA GTT CGC TGG TTG Phe Leu Lys Glu Tyr His Tyr Lys Gln Lys Val Arg Val Trp Leu			1700

	515	520	525	
	GAA CGA GAA CCA GTC AAG GCA AAG TAAACTCTCC GGTCCCCAAA GGGTGTAAAC			1754
5	Glu Arg Glu Pro Val Lys Ala Lys	530	535	
	TAGGTCCGCT TTCATGTGCA TCAGACAGTA CACCTATAGC AAGCACACGT AGCAGTGTAA			1814
10	GGCTTTCTCA TACAGTATGT AAGCTTAGTG TTAGTATCTG TCAGATGCTA CCTGCTGTAA			1874
	CTTATTCAAG TAAACATGGT GCCTATTGGA ACAATAGCGG ATAGAGCTAC AGGTGTTCAAG			1934
	TAAGACTACA AAAACATTTT GCCTATTTCG CTAACAGTTT GGTTTTAAAT GGCTGTGGTA			1994
15	TTTGAGTGAG GCAACCTGG GGCAATTGTT ATGAGAATT CTATTTCTTA CTGAAGAACAA			2054
	ATAATTAAT ATTGGATGAG TATTCACAA GTGTGACTAA TGTTGAAAT TATTTTTCC			2114
20	TAAGAGTTT TCCTATAACC TTCCAAAGT CGTGTGTTT GTAGTTACCA TAATCCAGCT			2174
	TTGAAGTCCA AAAGGATTAA AGGCCGCCTC CCTTGAAA ATGCCATTTC CGGCCCAAG			2234
	GCCTAGTGCC GTCCTCCCGG			2254

25 (2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
 30 (A) LENGTH: 536 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met	Asp	Lys	Val	Gly	Lys	Met	Trp	Asn	Asn	Leu	Lys	Tyr	Arg	Cys	Gln	
						5				10					15	
40	Asn	Leu	Phe	Ser	His	Glu	Gly	Gly	Ser	Arg	Asn	Glu	Asn	Val	Glu	Met
						20				25				30		
45	Asn	Pro	Asn	Arg	Cys	Pro	Ser	Val	Lys	Glu	Lys	Ser	Ile	Ser	Leu	Gly
						35			40				45			
	Glu	Ala	Ala	Pro	Gln	Gln	Glu	Ser	Ser	Pro	Leu	Arg	Glu	Asn	Val	Ala
						50			55			60				
50	Leu	Gln	Leu	Gly	Leu	Ser	Pro	Ser	Lys	Thr	Phe	Ser	Arg	Arg	Asn	Gln
						65			70			75			80	
	Asn	Cys	Ala	Ala	Glu	Ile	Pro	Gln	Val	Val	Glu	Ile	Ser	Ile	Glu	Lys
						85			90			95				
55	Asp	Ser	Asp	Ser	Gly	Ala	Thr	Pro	Gly	Thr	Arg	Leu	Ala	Arg	Arg	Asp
						100			105			110				
60	Ser	Tyr	Ser	Arg	His	Ala	Pro	Trp	Gly	Gly	Lys	Lys	His	Ser	Cys	
						115			120			125				
	Ser	Thr	Lys	Thr	Gln	Ser	Ser	Leu	Asp	Thr	Glu	Lys	Lys	Phe	Gly	Arg
						130			135			140				
	Thr	Arg	Ser	Gly	Leu	Gln	Arg	Arg	Glu	Arg	Arg	Tyr	Gly	Val	Ser	Ser

145	150	155	160
Met Gln Asp Met Asp Ser Val Ser Ser Arg Ala Val Gly Ser Arg Ser	165	170	175
5			
Leu Arg Gln Arg Leu Gln Asp Thr Val Gly Leu Cys Phe Pro Met Arg	180	185	190
10	195	200	205
His Leu Ser Glu Leu Met Leu Glu Lys Cys Pro Phe Pro Ala Gly Ser	210	215	220
15	Asp Leu Ala Gln Lys Trp His Leu Ile Lys Gln His Thr Ala Pro Val	225	230
20	235	240	
Ser Pro His Ser Thr Phe Phe Asp Thr Phe Asp Pro Ser Leu Val Ser	245	250	255
25	Thr Glu Asp Glu Glu Asp Arg Leu Arg Glu Arg Arg Arg Leu Ser Ile	260	265
30	270		
Glu Glu Gly Val Asp Pro Pro Pro Asn Ala Gln Ile His Thr Phe Glu	275	280	285
35	Ala Thr Ala Gln Val Asn Pro Leu Phe Lys Leu Gly Pro Lys Leu Ala	290	295
40	300		
Pro Gly Met Thr Glu Ile Ser Gly Asp Ser Ser Ala Ile Pro Gln Ala	305	310	315
45	320		
Asn Cys Asp Ser Glu Glu Asp Thr Thr Leu Cys Leu Gln Ser Arg	325	330	335
50			
Arg Gln Lys Gln Arg Gln Ile Ser Gly Asp Ser His Thr His Val Ser	340	345	350
55			
Arg Gln Gly Ala Trp Lys Val His Thr Gln Ile Asp Tyr Ile His Cys	355	360	365
60			
Leu Val Pro Asp Leu Leu Gln Ile Thr Gly Asn Pro Cys Tyr Trp Gly	370	375	380
65			
Val Met Asp Arg Tyr Glu Ala Glu Ala Leu Ser Glu Gly Lys Pro Glu	385	390	395
70	400		
Gly Thr Phe Leu Leu Arg Asp Ser Ala Gln Glu Asp Tyr Leu Phe Ser	405	410	415
75			
Val Ser Ser Ala Ala Thr Thr Gly Ser Leu His Ala Arg Ile Glu Gln	420	425	430
80			
Trp Asn His Asn Phe Ser Phe Asp Ala His Asp Pro Cys Val Phe His	435	440	445
85			
Ser Ser Thr Val Thr Gly Leu Leu Glu His Tyr Lys Asp Pro Ser Ser	450	455	460
90			
Cys Met Phe Phe Glu Pro Leu Leu Thr Ile Ser Leu Asn Arg Thr Phe	465	470	480
95			
Pro Phe Ser Leu Gln Tyr Ile Cys Arg Ala Val Ile Cys Arg Cys Thr	485	490	495

Thr Tyr Asp Gly Ile Asp Gly Leu Pro Leu Pro Ser Met Leu Gln Asp
 500 505 510

5 Phe Leu Lys Glu Tyr His Tyr Lys Gln Lys Val Arg Val Arg Trp Leu
 515 520 525

Glu Arg Glu Pro Val Lys Ala Lys
 530 535

10 (2) INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2206 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

20 (ii) MOLECULE TYPE: cDNA

- (ix) FEATURE:
 - (A) NAME/KEY: CDS
 - (B) LOCATION: 2..1375

25 (ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 2078
- (D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T, or G at positions: 2078, and 2116."

30 (ix) FEATURE:

- (A) NAME/KEY: misc_feature
- (B) LOCATION: 2063
- (D) OTHER INFORMATION: /note= "Nucleotide may be G or C at position 2063."

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

G GAG CGC GGC CTG GAG ACT AAC AGC TGC TCG GAA GAG GAG CTC AGC 46
 Glu Arg Gly Leu Gly Thr Asn Ser Cys Ser Glu Glu Glu Leu Ser
 1 5 10 15

45 AGC CCG GGT CGC GGA GGA GGA GGG GGC CGG CTT CTG CTG CAG CCC 94
 Ser Pro Gly Arg Gly Gly Gly Gly Arg Leu Leu Leu Pro
 20 25 30

50 CCA GGC CCT GAA TTA CCT CCG GTG CCC TTC CCG CTG CAG GAC TTG GTC 142
 Pro Gly Pro Glu Leu Pro Pro Val Pro Phe Pro Leu Gln Asp Leu Val
 35 40 45

55 CCT CTG GGG CGC CTG AGT AGA GGG GAG CAG CAG CAG CAG CAG CAG 190
 Pro Leu Gly Arg Leu Ser Arg Gly Glu Gln Gln Gln Gln Gln Gln
 50 55 60

60 CAA CCT CCC CCG CCC CCG CCT CCT CCC GGG CCC CTC CGG CCA CTC GCG 238
 Gln Pro Pro Pro Pro Pro Pro Gly Pro Leu Arg Pro Leu Ala
 65 70 75

GGT CCT TCT CGG AAG GGC TCC TTC AAA ATC CGC CTC AGT CGC CTC TTT
 Gly Pro Ser Arg Lys Gly Ser Phe Lys Ile Arg Leu Ser Arg Leu Phe
 80 85 90 95

	CGC ACC AAG AGC TGC AAC GGT GGC TCC GGC GGT GGG GAT GGG ACC GGC Arg Thr Lys Ser Cys Asn Gly Gly Ser Gly Gly Gly Asp Gly Thr Gly 100	334
5	AAG AGG CCT TCT GGA GAG CTG GCT GCT TCA GCT GCG AGC CTG ACA GAC Lys Arg Pro Ser Gly Glu Leu Ala Ala Ser Ala Ala Ser Leu Thr Asp 115	382
10	ATG GGA GGC TCT GCG GGC CGG GAG CTG GAC GCG GGG AGG AAA CCC AAG Met Gly Gly Ser Ala Gly Arg Glu Leu Asp Ala Gly Arg Lys Pro Lys 130	430
15	TTG ACA AGA ACT CAA AGT GCC TTT TCT CCG GTC TCC TTC AGC CCC CTG Leu Thr Arg Thr Gln Ser Ala Phe Ser Pro Val Ser Phe Ser Pro Leu 145	478
20	TTC ACA GGT GAA ACT GTG TCG CTT GTG GAT GTG GAC ATT TCT CAG CGG Phe Thr Gly Glu Thr Val Ser Leu Val Asp Val Asp Ile Ser Gln Arg 160	526
25	GGC CTG ACC TCT CCA CAC CCT CCA ACT CCC CCT CCT CCG AGA AGA Gly Leu Thr Ser Pro His Pro Pro Thr Pro Pro Pro Pro Arg Arg 180	574
30	AGC CTC AGC CTC CTA GAT GAT ATC AGT GGG ACG CTG CCT ACA TCT GTC Ser Leu Ser Leu Leu Asp Asp Ile Ser Gly Thr Leu Pro Thr Ser Val 195	622
35	CTT GTG GCT CGG ATG GGG TCT TCC TTG CAG TCT TTC CCC CTA CCT CCG Leu Val Ala Pro Met Gly Ser Ser Leu Gln Ser Phe Pro Leu Pro Pro 210	670
40	CCT CCT CCA CCC CAT GCC CCA GAT GCA TTT CCC CGG ATT GCT CCC ATC Pro Pro Pro Pro His Ala Pro Asp Ala Phe Pro Arg Ile Ala Pro Ile 225	718
45	CGA GCA GCT GAA TCC CTG CAC AGC CAA CCC CCA CAG CAC CTC CAG TGT Arg Ala Ala Glu Ser Leu His Ser Gln Pro Pro Gln His Leu Gln Cys 240	766
50	CCC CTC TAC CGG CCT GAC TCG AGC AGC TTT GCA GCC AGC CTT CGA GAG Pro Leu Tyr Arg Pro Asp Ser Ser Phe Ala Ala Ser Leu Arg Glu 260	814
55	TTG GAG AAG TGT GGT TGG TAT TGG GGG CCA ATG AAT TGG GAA GAT GCA Leu Glu Lys Cys Gly Trp Tyr Trp Gly Pro Met Asn Trp Glu Asp Ala 275	862
60	GAG ATG AAG CTG AAA GGG AAA CCA GAT GGT TCT TTC CTG GTA CGA GAC Glu Met Lys Leu Lys Gly Lys Pro Asp Gly Ser Phe Leu Val Arg Asp 290	910
	AGT TCT GAT CCT CGT TAC ATC CTG AGC CTC AGT TTC CGA TCA CAG GGT Ser Ser Asp Pro Arg Tyr Ile Leu Ser Leu Ser Phe Arg Ser Gln Gly 305	958
	ATC ACC CAC CAC ACT AGA ATG GAG CAC TAC AGA GGA ACC TTC AGC CTG Ile Thr His His Thr Arg Met Glu His Tyr Arg Gly Thr Phe Ser Leu 320	1006
	TGG TGT CAT CCC AAG TTT GAG GAC CGC TGT CAA TCT GTT GTA GAG TTT Trp Cys His Pro Lys Phe Glu Asp Arg Cys Gln Ser Val Val Glu Phe 340	1054
		345
		350

	ATT AAG AGA GCC ATT ATG CAC TCC AAG AAT GGA AAG TTT CTC TAT TTC Ile Lys Arg Ala Ile Met His Ser Lys Asn Gly Lys Phe Leu Tyr Phe 355	360	365	1102
5	TTA AGA TCC AGG GTT CCA CGA CTG CCA CCA ACT CCT GTC CAG CTG CTC Leu Arg Ser Arg Val Pro Gly Leu Pro Pro Thr Pro Val Gln Leu Leu 370	375	380	1150
10	TAT CCA GTG TCC CGA TTC AGC AAT GTC AAA TCC CTC CAG CAC CTT TGC Tyr Pro Val Ser Arg Phe Ser Asn Val Lys Ser Leu Gln His Leu Cys 385	390	395	1198
15	AGA TTC CGG ATA CGA CAG CTC GTC AGG ATA GAT CAC ATC CCA GAT CTC Arg Phe Arg Ile Arg Gln Leu Val Arg Ile Asp His Ile Pro Asp Leu 400	405	410	1246
	CCA CTG CCT AAA CCT CTG ATC TCT TAT ATC CGA AAG TTC TAC TAC TAT Pro Leu Pro Lys Pro Leu Ile Ser Tyr Ile Arg Lys Phe Tyr Tyr Tyr 420	425	430	1294
20	GAT CCT CAG GAA GAG GTA TAC CTG TCT CTA AAG GAA GCG CAG CTC ATT Asp Pro Gln Glu Glu Val Tyr Leu Ser Lys Glu Ala Gln Leu Ile 435	440	445	1342
25	TCC AAA CAG AAG CAA GAG GTG GAA CCC TCC ACG TAGCGAGGGG CTCCCTGCTG Ser Lys Gln Lys Gln Glu Val Glu Pro Ser Thr 450	455		1395
30	GTCAACACCA AGGGCATTTG GTTGCCAAGC TCCAGCTTTG AAGAACAAA TTAAGCTACC ATGAAAAGAA GAGGAAAAGT GAGGGACAGC GAAGGTTGGG ATTCTCTGTG CAGAGACTTT GGTTCCCCAC CGACGCCCTGG GGCTTGGAAAG AACGCACATGA CGCTACTCTG CGTGGGGCTC			1455
35	CACCTCACAC CCACCCCTGG GCATCTTAGG ACTGGAGGGG CTCCCTGGAA AACCTGAAAGA AGTCTCAACA CTGTTCTTT TTCAAAAAAA AAAAAAAAAGATGCGGCC GCAAGCTTAT			1515
40	TCCCTTTAGT GAGGGTTAAT TTAGCTTGG CACTGGCCGT CGTTTACAA CGTCTGTGACT GGGAAACCC TGGCGTTACC CAACTTAATC GCCTTGCAGC ACATCCCCCT TTGCCAGCT GGCGTAATAG CGAAGAGGCC CGCACCGATC GCCTTCCCA ACAGTGGGC AGCTGAATG			1575
45	GCGAATGGGA CGCGCCCTGT AGCGGGGCAT TAACGCCCGG CGGGTGTGGT GGTTACGCGC AGCGTGTACCG CTACACTTGC CAGCGCCCTA CGCCCGCTCC TTTCGCTTTC TTCCCTTCCT			1635
50	TTCTCGCCAC GTTCGCCGGC TTTCCTCGTC AACTCTAAAT CGGGGGCTCC CTTTAGGTTC CGATTTACTG CTTTACGCAC TCCACCCCAA AACTTGATTA GGTGATGTCA CTTATGGCAC			1695
55	CCCTGATAAC GTTCCCCCTT ACTTTGATCA CTTCCTTATA TGATCTTCC AATGAAACAT CACCTACTCG TCATCTTAT TAAAGATTT G			2055
				2115
				2175
				2206

(2) INFORMATION FOR SEQ ID NO:14:

60 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 458 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

5 Glu Arg Gly Leu Glu Thr Asn Ser Cys Ser Glu Glu Leu Ser Ser
1 5 10 15

10 Pro Gly Arg Gly Gly Gly Gly Arg Leu Leu Leu Gln Pro Pro
10 20 25 30

15 Gly Pro Glu Leu Pro Pro Val Pro Phe Pro Leu Gln Asp Leu Val Pro
15 35 40 45

20 Leu Gly Arg Leu Ser Arg Gly Glu Gln Gln Gln Gln Gln Gln
15 50 55 60

25 Pro Pro Pro Pro Pro Pro Pro Gly Pro Leu Arg Pro Leu Ala Gly
25 65 70 75 80

30 Pro Ser Arg Lys Gly Ser Phe Lys Ile Arg Leu Ser Arg Leu Phe Arg
20 85 90 95

35 Thr Lys Ser Cys Asn Gly Gly Ser Gly Gly Gly Asp Gly Thr Gly Lys
25 100 105 110

40 Arg Pro Ser Gly Glu Leu Ala Ala Ser Ala Ala Ser Leu Thr Asp Met
25 115 120 125

45 Gly Gly Ser Ala Gly Arg Glu Leu Asp Ala Gly Arg Lys Pro Lys Leu
30 130 135 140

50 Thr Arg Thr Gln Ser Ala Phe Ser Pro Val Ser Phe Ser Pro Leu Phe
35 145 150 155 160

55 Thr Gly Glu Thr Val Ser Leu Val Asp Val Asp Ile Ser Gln Arg Gly
35 165 170 175

60 Leu Thr Ser Pro His Pro Pro Thr Pro Pro Pro Pro Pro Arg Arg Ser
40 180 185 190

65 Leu Ser Leu Leu Asp Asp Ile Ser Gly Thr Leu Pro Thr Ser Val Leu
45 195 200 205

70 Val Ala Pro Met Gly Ser Ser Leu Gln Ser Phe Pro Leu Pro Pro Pro
45 210 215 220

75 Pro Pro Pro His Ala Pro Asp Ala Phe Pro Arg Ile Ala Pro Ile Arg
50 225 230 235 240

80 Ala Ala Glu Ser Leu His Ser Gln Pro Pro Gln His Leu Gln Cys Pro
55 245 250 255

85 Leu Tyr Arg Pro Asp Ser Ser Ser Phe Ala Ala Ser Leu Arg Glu Leu
60 260 265 270

90 Glu Lys Cys Gly Trp Tyr Trp Gly Pro Met Asn Trp Glu Asp Ala Glu
65 275 280 285

95 Met Lys Leu Lys Gly Lys Pro Asp Gly Ser Phe Leu Val Arg Asp Ser
70 290 295 300

100 Ser Asp Pro Arg Tyr Ile Leu Ser Leu Ser Phe Arg Ser Gln Gly Ile
75 305 310 315 320

Thr His His Thr Arg Met Glu His Tyr Arg Gly Thr Phe Ser Leu Trp
325 330 335

5 Cys His Pro Lys Phe Glu Asp Arg Cys Gln Ser Val Val Glu Phe Ile
340 345 350

Lys Arg Ala Ile Met His Ser Lys Asn Gly Lys Phe Leu Tyr Phe Leu
355 360 365

10 Arg Ser Arg Val Pro Gly Leu Pro Pro Thr Pro Val Gln Leu Leu Tyr
370 375 380

Pro Val Ser Arg Phe Ser Asn Val Lys Ser Leu Gln His Leu Cys Arg
385 390 395 400

15 Phe Arg Ile Arg Gln Leu Val Arg Ile Asp His Ile Pro Asp Leu Pro
405 410 415

Leu Pro Lys Pro Leu Ile Ser Tyr Ile Arg Lys Phe Tyr Tyr Tyr Asp
20 420 425 430

Pro Gln Glu Glu Val Tyr Leu Ser Leu Lys Glu Ala Gln Leu Ile Ser
435 440 445

25 Lys Gln Lys Gln Glu Val Glu Pro Ser Thr
450 455

(2) INFORMATION FOR SEQ ID NO:15:

30 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1390 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: cDNA

40 (ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 453..1388

45 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 108
(D) OTHER INFORMATION: /note= "Nucleotide may be A, C, T,
or G at positions: 108, and 109."

50 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 236
(D) OTHER INFORMATION: /note= "Nucleotide may be A or G at
positions: 236, 238, and 1258."

55 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 233
(D) OTHER INFORMATION: /note= "Nucleotide may be G or T at
position 233."

60 (ix) FEATURE:
(A) NAME/KEY: misc_feature
(B) LOCATION: 234
(D) OTHER INFORMATION: /note= "Nucleotide may be G or C at

position 234."

5 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 237
 (D) OTHER INFORMATION: /note= "Nucleotide may be C or T at
 position 237."

10 (ix) FEATURE:
 (A) NAME/KEY: misc_feature
 (B) LOCATION: 239
 (D) OTHER INFORMATION: /note= "Nucleotide may be A or T at
 position 239."

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CGGACGCGCTG	GGTTGGCTG	TGAATATTCT	ATTGCTTGC	AGTATCTGTT	TCTCTTCCTA	60	
20 GGCTCAAGTT	GGTGAACCAA	GCCTATTGTA	AAACAAGTGT	TATTCACCG	GGAGATGCCA	120	
	ATGGAGTAAC	AATTGTTAA	CCTTACGTT	TCTGCTGTA	TATTTTTTTA	AAAATCTGTT	180
25 AGTTTCTGGA	AAAAAAAGAG	AAAGGGGTTT	GTAGTACTTA	ACCCATTGTTA	TTGCCACGAG	240	
	TTTTAGTTAA	TTAGTTTTG	GAATAATGG	ATTTCAGTAT	AGCTTGTGG	TTAAATTGCA	300
30 TTGCCTTAT	TTATGTTTA	GGCTTATTTT	AAATTAAACA	TTAACAGAA	ACATTGAAA	360	
	TAGAATTTC	ATGCTGCCT	TAATTAACCT	AAAGACTGAT	TTTAATCTGA	CTATGACACT	420
35	GAGCATATTC	TTAAATTAC	TCATAATTAA	TA ATG CTT AAT ATA ATC TTA ATT			473
			Met Leu Asn Ile Ile Leu Ile	1	5		
	AAA TTT AGC AGT TTT AGT ATA AGA TGT	GCC ATT TTG	TCC TCT GTA TGT				521
	Lys Phe Ser Ser Phe Ser Ile Arg Cys Ala Ile Leu Ser Val Cys	10	15	20			
40	CTG AAT GAA GCT ATA ACA TTT GCC TTT TTA TTG	CAG GTT TTC	CTT CTT TGG				569
	Leu Asn Glu Ala Ile Thr Phe Ala Phe Leu Leu Gln Val Phe Leu Trp	25	30	35			
45	AAT ATG GAT AAA TAC ACC ATG ATA CGG AAA CTA GAA GGA CAT CAC CAT						617
	Asn Met Asp Lys Tyr Thr Met Ile Arg Lys Leu Glu Gly His His	40	45	50	55		
	GAT GTG GTA GCT TGT GAC TTT TCT CCT GAT GGA GCA TTA CTG GCT ACT						665
50	Asp Val Val Ala Cys Asp Phe Ser Pro Asp Gly Ala Leu Leu Ala Thr	60	65	70			
	GCA TCT TAT GAT ACT CGA GTA TAT ATC TGG GAT CCA CAT AAT GGA GAC						713
	Ala Ser Tyr Asp Thr Arg Val Tyr Ile Trp Asp Pro His Asn Gly Asp	75	80	85			
55	ATT CTG ATG GAA TTT GGG CAC CTG TTT CCC CCA CCT ACT CCA ATA TTT						761
	Ile Leu Met Glu Phe Gly His Leu Phe Pro Pro Pro Thr Pro Ile Phe	90	95	100			
60	GCT GGA GGA GCA AAT GAC CGG TGG GTA CGA TCT GTA TCT TTT AGC CAT						809
	Ala Gly Gly Ala Asn Asp Arg Trp Val Arg Ser Val Ser Phe Ser His	105	110	115			
	GAT GGA CTG CAT GTT GCA AGC CTT GCT GAT GAT AAA ATG GTG AGG TTC						857

	Asp Gly Leu His Val Ala Ser Leu Ala Asp Asp Lys Met Val Arg Phe		
120	125	130	135
5	TGG AGA ATT GAT GAG GAT TAT CCA GTG CAA GTT GCA CCT TTG AGC AAT Trp Arg Ile Asp Glu Asp Tyr Pro Val Gln Val Ala Pro Leu Ser Asn	140	145 150
10	GGT CTT TGC TGT GCC TTC TCT ACT GAT GGC AGT GTT TTA GCT GCT GGG Gly Leu Cys Cys Ala Phe Ser Thr Asp Gly Ser Val Leu Ala Ala Gly	155	160 165
15	ACA CAT GAC GGA AGT GTG TAT TTT TGG GCC ACT CCA CGG CAG GTC CCT Thr His Asp Gly Ser Val Tyr Phe Trp Ala Thr Pro Arg Gln Val Pro	170	175 180
20	AGC CTG CAA CAT TTA TGT CGC ATG TCA ATC CGA AGA GTG ATG CCC ACC Ser Leu Gln His Leu Cys Arg Met Ser Ile Arg Arg Val Met Pro Thr	185	190 195
25	CAA GAA GTT CAG GAG CTG CCC ATT CCT TCC AAG CTT TTG GAG TTT CTC Gln Glu Val Gln Glu Leu Pro Ile Pro Ser Lys Leu Leu Glu Phe Leu	200	205 210 215
30	TCG TAT CGT ATT TAG AAG ATT CTG CCT TCC CTA GTA GAA GGG ACT GAC Ser Tyr Arg Ile * Lys Ile Leu Pro Ser Leu Val Val Gly Thr Asp	220	225 230
35	AGA ATA CAC TTA ACA CAA ACC TCA AGC TTT ACT GAC TTC AAT TAT CTG Arg Ile His Leu Thr Gln Thr Ser Ser Phe Thr Asp Phe Asn Tyr Leu	235	240 245
40	TTT TTA AAG ACG TAG AAG ATT TAT TTA ATT TGA TAT GTT CTT CTA GTC Phe Leu Lys Thr * Lys Ile Tyr Leu Ile * Tyr Val Leu Val Leu	250	255 260
45	CAT TTT GAT CAG TTG AAG CTT TTA AAA TAT TAT TTA TAG ACA ATA GAA His Phe Asp Gln Leu Lys Leu Leu Lys Tyr Tyr Leu * Thr Ile Glu	265	270 275
50	GTA TTT CTG AAC ATA TCA AAT ATA AAT TTT TTT AAA GAT CTA ACT GTG Val Phe Leu Asn Ile Ser Asn Ile Asn Phe Phe Lys Asp Leu Thr Val	280	285 290 295
	AAT GG		1390
	Asn		

(2) INFORMATION FOR SEQ ID NO:16:

55 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 312 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

60 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Leu Asn Ile Ile Leu Ile Lys Phe Ser Ser Phe Ser Ile Arg Cys

1	5	10	15
Ala Ile Leu Ser Ser Val Cys Leu Asn Glu Ala Ile Thr Phe Ala Phe			
20	25	30	
5			
Leu Leu Gln Val Phe Leu Trp Asn Met Asp Lys Tyr Thr Met Ile Arg			
35	40	45	
Lys Leu Glu Gly His His Asp Val Val Ala Cys Asp Phe Ser Pro			
10 50	55	60	
Asp Gly Ala Leu Leu Ala Thr Ala Ser Tyr Asp Thr Arg Val Tyr Ile			
65	70	75	80
15 Trp Asp Pro His Asn Gly Asp Ile Leu Met Glu Phe Gly His Leu Phe			
85	90	95	
Pro Pro Pro Thr Pro Ile Phe Ala Gly Gly Ala Asn Asp Arg Trp Val			
100	105	110	
20 Arg Ser Val Ser Phe Ser His Asp Gly Leu His Val Ala Ser Leu Ala			
115	120	125	
Asp Asp Lys Met Val Arg Phe Trp Arg Ile Asp Glu Asp Tyr Pro Val			
25 130	135	140	
Gln Val Ala Pro Leu Ser Asn Gly Leu Cys Cys Ala Phe Ser Thr Asp			
145	150	155	160
30 Gly Ser Val Leu Ala Ala Gly Thr His Asp Gly Ser Val Tyr Phe Trp			
165	170	175	
Ala Thr Pro Arg Gln Val Pro Ser Leu Gln His Leu Cys Arg Met Ser			
180	185	190	
35 Ile Arg Arg Val Met Pro Thr Gln Glu Val Gln Glu Leu Pro Ile Pro			
195	200	205	
40 Ser Lys Leu Leu Glu Phe Leu Ser Tyr Arg Ile * Lys Ile Leu Pro			
210	215	220	
Ser Leu Val Val Gly Thr Asp Arg Ile His Leu Thr Gln Thr Ser Ser			
225	230	235	240
45 Phe Thr Asp Phe Asn Tyr Leu Phe Leu Lys Thr * Lys Ile Tyr Leu			
245	250	255	
Ile * Tyr Val Leu Val Leu His Phe Asp Gln Leu Lys Leu Leu Lys			
260	265	270	
50 Tyr Tyr Leu * Thr Ile Glu Val Phe Leu Asn Ile Ser Asn Ile Asn			
275	280	285	
55 Phe Phe Lys Asp Leu Thr Val Lys Asn Ile His Thr Cys Thr Tyr Leu			
290	295	300	
Asp Ile Ser Cys Tyr Met Leu Asn			
305	310		

60 (2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 257 amino acids
 - (B) TYPE: amino acid

(C) STRANDEDNESS: not relevant
 (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:
 Met Val Leu Cys Val Gln Gly Ser Cys Pro Leu Leu Ala Val Gln Gln
 1 5 10 15
 Ile Gly Arg Arg Pro Leu Trp Ala Gln Ser Leu Glu Leu Pro Gly Pro
 15 20 25 30
 Ala Met Gln Pro Leu Pro Thr Gly Ala Phe Pro Glu Glu Val Thr Glu
 35 40 45
 20 Glu Thr Pro Val Gln Ala Glu Asn Glu Pro Lys Val Leu Asp Pro Glu
 50 55 60
 Gly Asp Leu Leu Cys Ile Ala Lys Thr Phe Ser Tyr Leu Arg Glu Ser
 25 65 70 75 80
 Gly Trp Tyr Trp Gly Ser Ile Thr Ala Ser Glu Ala Arg Gln His Leu
 85 90 95
 30 Gln Lys Met Pro Glu Gly Thr Phe Leu Val Arg Asp Ser Thr His Pro
 100 105 110
 Ser Tyr Leu Phe Thr Leu Ser Val Lys Thr Thr Arg Gly Pro Thr Asn
 115 120 125
 35 Val Arg Ile Glu Tyr Ala Asp Ser Ser Phe Arg Leu Asp Ser Asn Cys
 130 135 140
 Leu Ser Arg Pro Arg Ile Leu Ala Phe Pro Asp Val Val Ser Leu Val
 40 145 150 155 160
 Gln His Tyr Val Ala Ser Cys Ala Ala Asp Thr Arg Ser Asp Ser Pro
 165 170 175
 45 Asp Pro Ala Pro Thr Pro Ala Leu Pro Met Ser Lys Gln Asp Ala Pro
 180 185 190
 Ser Asp Ser Val Leu Pro Ile Pro Val Ala Thr Ala Val His Leu Lys
 195 200 205
 50 Leu Val Gln Pro Phe Val Arg Arg Ser Ser Ala Arg Ser Leu Gln His
 210 215 220
 Leu Cys Arg Leu Val Ile Asn Arg Leu Val Ala Asp Val Asp Cys Leu
 55 225 230 235 240
 Pro Leu Pro Arg Arg Met Ala Asp Tyr Leu Arg Gln Tyr Pro Phe Gln
 245 250 255
 60 Leu

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 211 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

5

(ii) MOLECULE TYPE: peptide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Val Ala His Asn Gln Val Ala Ala Asp Asn Ala Val Ser Thr Ala
1 5 10 15

15

Ala Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser
20 25 30

20

Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Ala Val Pro Ala Pro
35 40 45

Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ala Asp Tyr
50 55 60

25

Arg Arg Ile Thr Arg Ala Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr
65 70 75 80

30

Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu
85 90 95

35

Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe
100 105 110

40

Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val
115 120 125

His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Ser Phe
130 135 140

45

Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg
145 150 155 160

Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu
165 170 175

50

Leu Cys Arg Gln Arg Ile Val Ala Thr Val Gly Arg Glu Asn Leu Ala
180 185 190

55

Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro
195 200 205

Phe Gln Ile
210

55 (2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 212 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

60

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

5 Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala
1 5 10 15

10 Ala Glu Pro Arg Arg Arg Ser Glu Pro Ser Ser Ser Ser Ser Ser
20 25 30

15 Ser Pro Ala Ala Pro Val Arg Pro Arg Pro Cys Pro Ala Val Pro Ala
35 40 45

20 Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ser Asp
50 55 60

25 Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe
65 70 75 80

30 Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala
85 90 95

35 Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys
100 105 110

40 Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg
115 120 125

45 Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr
130 135 140

50 Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg
145 150 155 160

55 Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln
165 170 175

60 Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu
180 185 190

65 Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe
195 200 205

70 Pro Phe Gln Ile
210

(2) INFORMATION FOR SEQ ID NO:20:

50 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 306 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: not relevant

55 (ii) MOLECULE TYPE: peptide

60 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Ala Leu Ser Pro Ala Ala Thr Leu Thr Ala Trp Pro Ala Asp Ser Ala
1 5 10 15

	Arg Arg Gly Pro Gly Cys Thr Ala Ser Gly Tyr Pro Val Pro Ala Ala
	20 25 30
5	Arg Ala Pro Ala Ala Gly Asp Gln Trp Val Thr Ala Ala Ala Arg Asp
	35 40 45
	Phe Val Ile Arg Pro Pro Gly Ser Gly Glu Lys Glu Pro His Pro Phe
	50 55 60
10	Ser Leu Cys His His Phe Gly His Pro Ala Gly Leu Val Leu Gly Phe
	65 70 75 80
15	Ala Leu Thr Ser Arg Lys Asp Ala Asn Pro Ser Leu Thr Pro Ala Arg
	85 90 95
	Ala Ala Thr Cys Leu Cys Arg Gly Asp Pro Ser Leu Met Thr Leu Arg
	100 105 110
20	Cys Leu Glu Pro Ser Gly Asn Gly Gly Glu Gly Thr Arg Ser Gln Trp
	115 120 125
	Gly Thr Ala Gly Ser Ala Glu Glu Pro Ser Pro Gln Ala Ala Arg Leu
	130 135 140
25	Ala Lys Ala Leu Arg Glu Leu Gly Gln Thr Gly Trp Tyr Trp Gly Ser
	145 150 155 160
	Met Thr Val Asn Glu Ala Lys Glu Lys Leu Lys Glu Ala Pro Glu Gly
30	165 170 175
	Thr Phe Leu Ile Arg Asp Ser Ser His Ser Asp Tyr Leu Leu Thr Ile
	180 185 190
35	Ser Val Lys Thr Ser Ala Gly Pro Thr Asn Leu Arg Ile Glu Tyr Gln
	195 200 205
	Asp Gly Lys Phe Arg Leu Asp Ser Ile Ile Cys Val Lys Ser Lys Leu
	210 215 220
40	Lys Gln Phe Asp Ser Val Val His Leu Ile Asp Tyr Tyr Val Gln Met
	225 230 235 240
	Cys Lys Asp Lys Arg Thr Gly Pro Glu Ala Pro Arg Asn Gly Thr Val
45	245 250 255
	His Leu Tyr Leu Thr Lys Pro Leu Tyr Thr Ser Ala Pro Ser Leu Gln
	260 265 270
50	His Leu Cys Arg Leu Thr Ile Asn Lys Cys Thr Gly Ala Ile Trp Gly
	275 280 285
	Leu Pro Leu Pro Thr Arg Leu Lys Asp Tyr Leu Glu Glu Tyr Lys Phe
	290 295 300
55	Gln Val
	305

(2) INFORMATION FOR SEQ ID NO:21:

60 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 225 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: not relevant

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

10	Met Val Thr His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu	1	5	10	15
15	Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln	20	25	30	
20	Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp	35	40	45	
25	Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Ser Ala Glu Pro	50	55	60	
30	Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe	65	70	75	80
35	Ala Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln	85	90	95	
40	Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln	100	105	110	
45	Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val Tyr His Tyr Met	115	120	125	
50	Pro Pro Pro Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser	130	135	140	
55	Ser Glu Val Pro Glu Gln Pro Ser Ala Gln Pro Leu Pro Gly Ser Pro	145	150	155	160
60	Pro Arg Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu	165	170	175	
65	Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu	180	185	190	
70	Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr	195	200	205	
75	Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro	210	215	220	
80	Leu	225			

55 (2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 225 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: not relevant
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

5 Met Val Thr His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu
1 5 10 15

10 Asp Thr Ser Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln
20 25 30

15 Leu Val Val Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp
35 40 45

20 Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Leu Ser Ala Glu Pro
50 55 60

25 Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe
65 70 75 80

20 Thr Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln
85 90 95

25 Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
100 105 110

30 Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val His His Tyr Met
115 120 125

35 Pro Pro Pro Gly Thr Pro Ser Phe Ser Leu Pro Pro Thr Glu Pro Ser
130 135 140

35 Ser Glu Val Pro Glu Gln Pro Pro Ala Gln Ala Leu Pro Gly Ser Thr
145 150 155 160

40 Pro Lys Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu
165 170 175

40 Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
180 185 190

45 Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
195 200 205

45 Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
210 215 220

50 Leu
225

(2) INFORMATION FOR SEQ ID NO:23:

55 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 510 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: not relevant
(D) TOPOLOGY: linear

60 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Leu Tyr Trp Ser Ser Thr Val Val Ala Ala Ala Leu Glu Xaa Xaa Xaa
1 5 10 15

5 Xaa Xaa Gly Cys Xaa Xaa Xaa Glu Xaa Glu Gly Val Arg Ser Ser Pro
20 25 30

Val Val Ser Leu Ser Leu Pro Leu Xaa Arg Ala Arg Met Gly Arg Ala
35 40 45

10 Glu Leu Leu Glu Gly Lys Met Ser Thr Gln Asp Pro Ser Asp Leu Trp
50 55 60

Ser Arg Ser Asp Gly Glu Ala Glu Leu Glu Gln Asp Leu Gly Trp Tyr
15 65 70 75 80

His Gly Asn Leu Thr Arg His Ala Ala Glu Ala Leu Leu Leu Ser Asn
20 85 90 95

Gly Cys Asp Gly Ser Tyr Leu Leu Arg Asp Ser Asn Glu Thr Thr Gly
25 100 105 110

Leu Tyr Ser Leu Ser Val Arg Ala Lys Asp Ser Val Lys His Phe His
30 115 120 125

Val Glu Tyr Thr Gly Tyr Ser Phe Lys Phe Gly Phe Asn Glu Phe Ser
35 130 135 140

Ser Leu Lys Asp Phe Val Lys His Phe Ala Asn Gln Pro Leu Ile Gly
40 145 150 155 160

Ser Glu Thr Gly Thr Leu Met Val Leu Lys His Pro Tyr Pro Arg Lys
45 165 170 175

Val Xaa Glu Pro Ser Ile Tyr Glu Ser Val Arg Val His Thr Ala Met
50 180 185 190

Gln Thr Gly Arg Thr Glu Asp Asp Leu Val Pro Thr Ala Pro Ser Leu
55 195 200 205

Gly Thr Lys Glu Gly Tyr Leu Thr Lys Gln Gly Gly Leu Val Lys Thr
60 210 215 220

Trp Lys Thr Arg Trp Phe Thr Leu His Arg Asn Glu Leu Lys Tyr Phe
65 225 230 235 240

Lys Asp Gln Met Ser Pro Glu Pro Ile Arg Ile Leu Asp Leu Thr Glu
70 245 250 255

Cys Ser Ala Val Gln Phe Asp Tyr Ser Gln Glu Arg Val Asn Cys Phe
75 260 265 270

Cys Leu Val Phe Pro Phe Arg Thr Phe Tyr Leu Cys Ala Lys Thr Gly
80 275 280 285

Val Glu Ala Asp Glu Trp Ile Lys Ile Leu Arg Trp Lys Leu Ser Gln
85 290 295 300

Ile Arg Lys Gln Leu Asn Gln Gly Glu Ala Arg Ser Asp Leu Gly Arg
90 305 310 315 320

Ser Ser Leu Asn Arg Ser Phe Leu Pro Arg Asn Ala Leu Ala Gln Glu
95 325 330 335

	Gln Val Glu Cys Phe Pro Xaa Arg Cys Asp Leu Xaa Gln Leu Gln Met			
	340	345	350	
5	Lys Thr Asp Xaa Asp Phe Leu Ser Lys Thr Asn Gln Asn Arg Cys Xaa			
	355	360	365	
	Leu Gly Pro Ile Tyr His Val Ala Asp Ser Leu Cys Cys Pro Ser Xaa			
	370	375	380	
10	Met Leu Pro Xaa Pro Xaa Glu His Xaa Ser Asn His His Xaa Asp Arg			
	385	390	395	400
	Lys Cys Leu Asn His His Ser Xaa Val Cys Ser Leu Leu Glu His Thr			
	405	410	415	
15	Met Glu Glu Glu Gly Phe Leu Phe Ser Leu Ile Val Val Pro Lys Pro			
	420	425	430	
20	Ile Asp Thr Ser Cys Leu Glu Ser His Cys Glu Ser Trp Ser Ala Cys			
	435	440	445	
	Leu Thr Xaa Arg Leu Cys Tyr Xaa Pro Arg Arg Lys Gln Ile Leu Gly			
	450	455	460	
25	Gly Leu Asp Asp Xaa Cys Arg Ile Tyr Ile Gln Ile Glu Asn Ile Lys			
	465	470	475	480
	Tyr Phe Gln Gly Arg Gly Phe Phe Phe Xaa Phe Phe Pro Leu Tyr Thr			
	485	490	495	
30	Lys Lys Lys Lys Lys Leu Glu Gly Gly Pro Tyr Pro Xaa			
	500	505	510	
35	(2) INFORMATION FOR SEQ ID NO:24:			
	(i) SEQUENCE CHARACTERISTICS:			
	(A) LENGTH: 2093 base pairs			
	(B) TYPE: nucleic acid			
	(C) STRANDEDNESS: single			
40	(D) TOPOLOGY: linear			
	(ii) MOLECULE TYPE: cDNA			
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:			
	TAAGGTCCAC GTCGCTCCGM AGCCATCACT ACAGKMC CGC GCGTGGCCT CTGGGGCCCA		60	
50	CAAWCTCCGR GGAGACCTGC ATCAAGATGG AGGTGAGAGT CAAGGCCTTG GTTCAC TCTT		120	
	CCAGCCCGAG TCCAGCCCTG AATGGCGTCC GGAAGGATTT CCACGACCTC CAGTCTGAGA		180	
55	CCACGTGCCA GGAGCAAGCC AATTCACTGA AGAGCTCGGC TTCTCTATAAT GGAGACCTGC		240	
	ATCTTCACTT GGATGAACT GTGCCCTGTG TTATTGGACT TATGCCCTCAG GACTCACATTC		300	
60	AGTATACTGT GCTTTAGAT GAGGGGATGT ATCCCTTGGA AGGATCACGG AGCTATTGTC		360	
	TGGACAGCTC TTCTCCCATG GAAAGTCTCTG CGGTTCCCTC TCAAGTGGGA GGGCGCGCTT		420	
	TCCCCGAGGA TGAGAGTCAG GTAGACCAGG ACCTAGTTGT CGCCCCAGAG ATCTTCGTGG		480	

ATCAGTCCGT	GAATGGCTTG	TTGATTGGCA	CCACGGGAGT	CATGTTGCAG	AGCCCGAGAG	540	
CGGGTCACGA	TGATGTCCTC	CCACTCTCAC	CATTGCTACC	TCCAATGCAG	AATAATCAAA	600	
5	TCCAAAGGAA	CTTCAGTGGA	CTCACTGGCA	CAGAAGCCCA	CGTGGCTGAA	AGTATGCGCT	660
	GTCATTTGAA	TTTTGATCCG	AACTCTGCTC	CTGGGGTTGC	AAGAGTTTAT	GACTCAGTGC	720
10	AAAGTAGTGG	TCCCAGTGGT	GTGACAAGCC	TTACAGAGGA	GCTGAAAAAA	CTTGCAAAGC	780
	AAGGATGGTA	CTGGGGACCA	ATCACACGTT	GGGAGGCAGA	AGGAAAGCTA	GCAAACGTGC	840
15	CAGATGGTTC	TTTCTTGTG	CGGGACAGTT	CTGACGACCG	TTACCTTTTA	AGCTTGTAGCT	900
	TTCGCTCCA	TGGTAAACAA	CTTCACACTA	GAATTGAGCA	CTCAAATGGT	AGGTTTAGCT	960
20	TTTATGAACA	GCCAGATGTG	GAAAGGACAT	ACTCCATAGT	TGATCTAATT	GAGCATTCCA	1020
	TCCAGGACT	CGAAARTGGA	GCTTTTGTT	ATTCAAGTC	TCGGCTGCCT	GGATCTGCAA	1080
25	CTTACCCCGT	CAGACTGACC	AAACCCAGTGT	CCCGGTTCAT	GCAGGTGCGC	TCGTTGAGCT	1140
	ACCTGTGTCG	TTTTGTTATA	CGTCAGTATA	CCAGAACAGA	CTTAATTCTAG	AAACTGCCTT	1200
30	TGCCAAACAA	AATGAAGGAT	TATTTACAGG	AGAACAGACTA	CTGAAAGATT	GAGAACCCCTG	1260
	CATCTGAC	TTTGGGAATA	AGAACAAAGAG	ATTGAAATAC	AGTTTACAAA	CTTTCATTGC	1320
35	CATCAAAATC	TTTGCTGCC	ATAACTATT	CAGTTTATG	TGAAAAGAG	TCATCAGTT	1380
	GTTTAGGGGT	GGGGAAAGTGT	CAGCAAGGTG	TCTGGGTTT	ATTTGGTTC	TTTAAAAAAAG	1440
40	AAAGTCTG	AAGTTTCTAGA	RGTGTTGAAT	TATGTTTCAT	CAATGTGCAG	AATAATCACA	1500
	ATGTGAATT	TCAAATTCTC	CTCAATGCC	CCCCGCCCA	KTCCTTGCT	GCTATCCACT	1560
45	GTGATTTTTA	TGCACTAAAA	GCMCATTTCA	TGKTTTTCA	ACCTTAAGTA	AAGTGAATG	1620
	AAACTTAACR	GAATGGAAAT	TGCTATTCT	TTTTAAATGG	YCCATTTC	AAAMARGTG	1680
50	TTGAATAAMC	AWMCCTGKT	GAATAAAACM	MGRAWTTWMM	WWTARCAMYG	BAGRTRGRGTT	1740
	TTTAATCTYY	TAMYTTDAAA	AGATTATTT	AGAATYGGKA	ATTGACMIAA	TATGGGTWA	1800
55	TBGGRMCGGR	GATCTGSAAC	ATATKYTTTA	ACAACAWTTT	WTKKCYTTA	ATKKDTTTY	1860
	AARGKTTGBC	TTATTWHTTT	GGBKBBVAA	AGKWBVAHTT	CTCYGTYSCC	YTCGTTTC	1920
60	TCTTCTAGTT	TGTGNTTATT	TAATAATGG	CCTTACATTA	AAAATTGTA	AAGAAATGTA	1980
	TACCACCAAT	TTAGAAATTG	TTGCCCTTT	TGTAATTTAA	CTCGGGTACA	AATNGGCATA	2040
	ACATGAAAAC	CTATGGAAC	AGAATTATTA	TTAAAGAAAT	ATTAGATGAT	CAT	2093

55 (2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1748 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

60 (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

5	ATGGAGGCCG GAGAGGAACC GCTGCTGCTG GCCGAACCTCA AGCCCGGGCG CCCCCACCAG	60
	TTTGATTTGA AGTCACAGCTG TGAACCTGG AGCGTGGCT TCTCGCCAGA CGGTCTCTGG	120
10	TTCGCTCTGGT CTCAGGACCA CTGCGTGGTC AAAGCTGGT CCTCGCCCTT AGAGAACAG	180
	TTCATCCCTA AAGGATTGCGA AGCCAAGAGC CGAACAGAGC AGAATGACCC AAAAGGACCG	240
15	GGCAGTCTGA AGGAGAAGAC GCTGGACTGT GGCCAGATTG TGTTGGGGCT GGCCCTCAGC	300
	CCATGGCCCT CTCCACCCAG CAGGAAACTC TGCGCACGTC ACCATCCCCA GGCGCTGTAT	360
	GTTCCTTGCG TGATCCTGGC CACAGGTCTC AACAGATGGC AGATCAAGAT TTGGAGGTA	420
20	CAGACAGGCC TCCGCTCTCT GAATCTTTCT GGCCACCAAG ACGTCGTGAG AGATCTGAGC	480
	TTCACGGCCA GCGGCAGTTT GATTTTGTC TCTGCATCCC GGGATAAGAC ACTTCGAATT	540
25	TGGGACCTGA ATAAGCAGCG TAAGCAGATC CAGGTGTAT CCAGGCATCT GCAGTGGTT	600
	TACTGCTGCT CCATCTCCCC TGACTGTAGC ATGCTGTGCT CTGCAGCTGG GGAGAAGTCG	660
	GTCTTCTGTG GGAGCATGCG GTCCCTACACA CTAACTGGGA AACTAGAAGG CCACCAAAGC	720
30	AGTGTGTCT CCTGTGATTCT CTCTCCTGTAT TCAGCCTTGTC TTGTCACAGC TTGCTATGAC	780
	ACCAAGTGTGA TTATGTGGGA CCCCTACACC GGCGAGAGGC TGAGGTCACT TCATCACACA	840
35	CAGCTTGAAAC CCACCATGGA TGACAGTGAC GTCCACATGA GTCCTCTGAG GTCCGTGTGC	900
	TTCTCCTGAG AGGCTTGTGA TCTCGCTACG GTGCCAGATG ACAGRCGTGCT CAGGATCTGG	960
	GCTCTGGAAAC TGAAAGCTCC GGTTGCTTT GCTCCGATGA CCAATGGTCT TTGCTGCACA	1020
40	TTTTTYCCAAAYGGTGAAT YATTGCCACA GGACAAAGAG ATGGCCACGT CCAGTCTCTGG	1080
	ACAGCTCTTA GGGCTCTGTC CTCACTGAG CACTTATGCC GGAAGGCCCT TCAGAAGTTTC	1140
	CTAACAACTT ACCAAGCTCC AGCACTGCCA ATCCCCAAGA AAATGAAAGA GTTCCCTCACA	1200
45	TACAGGACTT TTAAAGCAAC ACCACATCTT GTGCTTCTTT GTAGCAGGGT AAATCGTCTT	1260
	GTCAAAGGGG GTGCTGGAA TAATGGGCCA AACATCTGGT CTTGCTATTGA AATAGCATT	1320
50	CTTTGGGATT GTGAATAGAA TGTAGAAAAA CCAGATTCCA GTGTAACGTAGT CATGGRCTTT	1380
	TCTCTCCCTG GGCGATGTGGA AAGTCAGTCT TAGGAGGGAA GGAGATTCCA CTTGKACGG	1440
55	GCAACAGAGC CYTTACGTTT AAATTTTCA GTCCAGTTAT KGAACAGCAA GTGTTTGAAM	1500
	TCTTCTGGY TTGTTTGTGA WTTCAAAAGTG GCAGTTACTG RWKGTTGTTT TTGGATTAT	1560
	GGCAACYAAAG TTAGGGCTC CAGNGGTTNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN	1620
60	NNNNNNNNNNN NNNNNNNNNN NNNNNNNNNNT HNAIBNVNRNN NRTNNNNRMA TNNNNNNNNN	1680
	NNNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN	1740
	NNNNNNNNNN	1748

(2) INFORMATION FOR SEQ ID NO:26:

5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2198 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: cDNA

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

GGCGGTGGTG	ATGGCGGCAG	GCGCTCGGAC	AGCTCCGCTT	GAGCTGAGCT	CGGAGAGATC	60
CCTCCAGAAA	GTGCCAGAAA	GAAACTTCCT	CTTAGAGAAAAG	CTGAAAACAC	AATATTATA	120
20 ACACCTGGAAA	TTGTAAAGAA	TTTGTGTTAA	ATGGCTGAAA	ACAATAGTAA	AAATGAGAT	180
GTACGGGCTA	AAACAAGTCG	GAGTCGAAGT	GCTGACAGGA	AGGATGGTTA	TGTGTGGAGT	240
25 GGAAAGAAAGT	TGTCTGGTCA	AAAAAGAGT	GAGAGTTGTT	CTGAATCTGA	AGCCAAGAAA	300
GGGCAGCTTA	GTCGTTGTC	CATTGAGTTG	GACTTGAATC	ATTCCTGTGG	GCATAGATTT	360
30 TTAGGCCAT	CCCTTAAACA	GAAACTGCAA	GATGGGGTGG	GGCAGTGTTT	TCCAATAAG	420
AATTGTAGTG	GCCGACACTC	TCCAGGGCTT	CCATCTAAA	GAAAGATTC	TATCAGTGA	480
CTCATGTTAG	ATAMGTGYSC	YTTCACCT	CGCTCAGATT	TAGCCTTTAG	GTGGCATTTT	540
35 ATTAACACGAC	ACACTGTTCC	TATGAGTCCC	AACTCAGATG	AATGGGTGAG	TGCAGACCTG	600
TCTGAGAGGA	AACTGAGAGA	TGCTCAGCTG	AAACGAAGAA	ACACAGAAGA	TGACATACCC	660
40 TGTTTCTCAC	ATACCAATGG	CCAGCCTTGT	GTCTAACTG	CCAACAGTGC	TTCGTGTACA	720
GGTGGTCACA	TAACTGGTTC	TATGATGAAC	TTGGTCACAA	ACAACAGCAT	AGAAGACAGT	780
GACATGGATT	CAGAGGATGA	AATTATAACG	CTGTGCACAA	GCTCCAGAAA	AAGGATATAAG	840
45 CCCAGGTGGG	AAATGGAAGA	GGAGATCCTG	CAGTTGGAGG	CACCTCCCAA	GTTCCACACC	900
CAGATCGACT	ACGTCCACTG	CCTGTTCAC	GACCTCCCTTC	AGATCAGTAA	CAATCCGTGC	960
50 TACTGGGGTG	TCATGGACAA	ATATGAGGCC	GAAGCTCTGC	TGGAAGGAAA	GGCAGAGGGC	1020
ACCTTTTAC	TTCGAGATTG	AGCGCAGGAA	GATTATTTT	TCTCTGTGTTAG	TTTTAGACGC	1080
TACAGTCGTT	CTCTTCATGC	TAGAATTGAG	CAGTGGAAATC	ATAACTTTAG	CTTTGATGCC	1140
55 CATGATCCTT	GTGTCTTCCA	TTCTCCTGAT	ATTACTGGGC	TCCTGGAAACA	CTATAAGGAC	1200
CCCCAGTGCCT	GTAATGTTCTT	TGAGCCGCTC	TTCTCCACTG	CCTTAATCCG	GACGTTCCCC	1260
60 TTTTCCTTGC	AGCATATTG	CAGAACGGTT	ATTGTAAATT	GTACGACTTA	CGATGGCCTC	1320
GATGCCCTTC	CCATTCCTTC	GCCTATGAAA	TTGTATCTGA	AGGAATACCA	TTATAAATCA	1380
AAAGTTAGGT	TACTCAGGAT	TGATGTGCCA	GAGCAGCAGT	GATGCGGAGA	GGTTAGAATG	1440

TCKACCGGAG CTTTYGTTCC CTTTAGTGAG GGTTAATTTC GAGCTGGCG TAATCATGGT 1500
 CATAGCTGTT TCCTGTTGTA AATGYTYATC CGCTCACAAAT TCCACACAAC ATACGAGCCG 1560
 5 GAAGCATAAA GTGTAAGCC TGGGGTGCCT AATGAGTGAG CTAACTCACA TTAATGSGT 1620
 YCGCGTCACT GCCCGCTTTC CAGTCGGAA ACCTGTCGTG CCASCTGCAT TAMTGAATCN 1680
 10 GCCAACKGCG NGGGANAGCG GTTNGCNTAT TGGGCCTCT TCACCTCNC GCTCACTGAN 1740
 TCNCTNCCTC GGTCNTTCGN TGCTGCTACN GTNTCCCCA TCCAAGCGTT ATACGCTATC 1800
 CNCAGAACTG GGAAANNNCNG AANACNNNTNA CAAAGCTCAN TGCTANCGTA NACGCCNTGC 1860
 15 NGGCTTTCC TCGTCCCCN ACACNCTAAA CAGCCCTCGA GTGCAACCNC GATATANATN 1920
 TCTTCCCTNA ACCCCTGCCT CTGTCNCGC CTNCGACTTC GCTTCCNNNG ATTGCTTTCN 1980
 20 CCCCGTAGTC NGTCNTAGTG NGCNGCGCT TCCACCCCTTC NACCNCTAGG TANNNNNNANN 2040
 CNCCAAANCC NCCNCCCCTC NGATAAAAAG TNAGNGCCTT NANNNCNNNG ATAAAAATGG 2100
 TCCCNACTT TCCAATGTCT NCCNCCCCG 3NNTCTNGCC ACCCAANTNA NNTTCCGGN 2160
 25 ACTGNATCCG GTGCTANCNT CCTGTTCTC CTCCCNCC 2198

(2) INFORMATION FOR SEQ ID NO:27:

30 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2254 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: cDNA

40 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CTCGGGGCCGG GATGGATCCG CCGGGAAAGAG GAAGACAAGC GGAGCGTTGA CCCCTGCGC 60
 45 ACGGTGCCCC CGCGCTAGTG GGAGCTTACT CCCAGTAGCT CTCGCTCTT TAATCAATGG 120
 ATAAAGTGGG GAAAATGTGG AACAACTTAA AATACAGATG CCAGAATCTC TTCAGCCACG 180
 AGGGAGGAAG CCGTAATGAG AACGTGGAGA TGAACCCAA CAGATGTCCG TCTGTCAAAG 240
 50 AGAAAAGCAT CAGTCGGGA GAGGCAGCTC CCCAGCAAGA GAGCAGTCCTC TTAAGAGAAA 300
 ATGTTGCCTT ACAGCTGGGA CTGAGCCCTT CCAAGACCTT TTCCAGGCGG ACCAAAAACT 360
 55 GTGCCGCAGA GATCCCTAA GTGGTTGAAA TCAGCATCGA GAAAGACAGT GACTGGGTG 420
 CCACCCCAGG AACGAGGCTT GCACGGAGAG ACTCCTACTC GCGGCACGCC CCGGGGGAG 480
 GAAAGAAGAA ACATTCCTGT TCCACAAAGA CCCAGAGTTC ATTGGATACCG GAGAAAAAGT 540
 60 TTGGTAGAAC TCGAAGCGGC CTTCAGAGGC GAGAGCGCG CTATGGAGTC AGCTCCATGC 600
 AGGACATGGA CAGCGTTCTC AGCCGCGCGG TCGGGAGCGG CTCCCTGAGG CAGAGGCTCC 660
 AGGACACGGT GGGTTTGTTGTG TTTCCCATGA GAACCTTACAG CAAGCAGTCA AAGCCACTCT 720

	TTTCCAATAA AAGAAAAATM CATCTYTCTG AATTAATGCT KGAGAAATGC CCTTTTCCGT	780
5	CTGGCTCRGA TTTAGCMCAA AAGTGGCATT TGATTAACCA GCATACAGCT CCTGTGAGCC	840
	CACATTCAAC ATTTTTGAT ACRTTTGATC CATCTTGGGT TTCTACAGAA GATGAAGAAG	900
	ATAGGCTTAG AGAGAGAAGG CGGCTTAGTA TTGAGAAGG GTTGTATCCC CCTCCCAATG	960
10	CACAAATACA TACATTTGAA GCTACTGCAC AGGTTAATCC ATTATTAAA CTGGGACCAA	1020
	AATTAGCTCC TGGAAATGACT GAAATAAGTG GGGACAGTTC TGCATTTC CAAGCTAATT	1080
15	GTGACTCGGA AGAGGATACA ACCACCCGTG GTTGGAGTC ACGGAGGCAG AAGCAGCGTC	1140
	AGATATCTGG AGACAGCCAT ACSCATGTTA GCAGACAGGG ACCTTGGAAA GTCCACACAC	1200
	AGATTGATTA CATAACTGTC CTCTGCGCTG ATTGCTTCA AATTACAGGG AATCCCTGTT	1260
20	ACTGGGGAGT GATGGACCGT TATGAAGCAG AAGCCCTCTC CGAAGGGAAA CCKGAAGGCA	1320
	CGTTCTTGTG CAGGGACTCT GCACAGGAGG ACTACCTCTT CTCTGTGAGT TCCGGCCGTA	1380
25	CAACAGGATC TCTGCACGCC CGGATCGAGC AGTGGAACCA CAACTTCAGC TTGATGCCC	1440
	ATGACCCCTG CGTGTTCACAY TCCTCCACTG TCACGGGGT TCTCGAACAC TATAAAAGAYC	1500
	CCAGTTCKTG CATGTTTTT GAACCGTTGC TAACGATATC ACTSAATAGR ACTTCCCTT	1560
30	TCAGCCCTGCA GTATATCTGC CGCGCAGTGA TCTGCAGATG CACTACGTAT GATGGGATTG	1620
	ACGGGCTCCC CCTACCGCTCG ATGTTACAGG ATTTTTTAAA AGAGTATCAT TATAAAACAAA	1680
35	AAGTTAGAGT TCGCTGGTTG GAACGAGAAC CAGTCAAGGC AAAGTAAACT CTCCGGTCCC	1740
	CAAAGGGTGT TAACTAGGTC CCTTTTCATG TGCACTCAGAC AGTACACCTA TAGCAAGCAC	1800
	ACGTTAGCAGT GTTACGGTTT TTCATACAGT ATGTAAGCTT AGTGTGAGT TCTGTAGAT	1860
40	GCTACCTGCT GTTACTTATT CAGATAAACCA TGTTGCCTAT TGGAAACAATA GCGGATAGAG	1920
	CTACAGGTGT TCAGTAAGAC TACAAAAACA TTGCTTCTAT TTGCTAACAA GTTTGGTTT	1980
	TAATGGCTGT GGTATTGAG TGAGGCAAYY CTGGGGCATT TGTTATGAG AATTCTATTT	2040
45	CTTACTGAAG AACAAATWAT TAATATTGGA TGAGTATTTC AACAGTGTGA CTAATGTTG	2100
	AAATTATTTT TTCTTAAGAG TTCTTCCWAT AACCTTCCMA AAGTCGTGAT GTTTGTAGTT	2160
50	ACCATAATCC AGCTTTGRAG TCCMAAARGA TTAAAGRCYD CCTCCCTTG RAAAATGCCA	2220
	TTTCYKGCCC CAAGGCCAG TGCGCGCCCT NCGG	2254

55 (2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2206 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

60 (ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

5	GGAGCGCGGC CTGGAGACTA ACAGCTGCTC GGAAGAGGAG CTCAGCAGCC CGGGTCGCGG	60
	AGGAGGAGGG GGCAGCCGGC TTCTGCTGCA GCCCCCAGGC CCTGAATTAC CTCCGGTGCC	120
10	CTTCCCGCTG CAGGACTTGG TCCCTCTGGG GCAGCTGAGT AGAGGGGAGC AGCAGCAGCA	180
	GCAGCAGCAG CAACCTCCCC CGCCCCCGCC TCCTCCGGG CCCCCCCGGC CACTCGCGG	240
	TCCTTCTCGG AAGGGCTCTC TCAAAATCCG CCTCAGTCGC CTCTTCTGCA CCAAGAGCTG	300
15	CAACGGTGGC TCCGGCGGTG GGGATGGGC CGGCAAGAGG CCTCTCTGGG AGCTGGCTGC	360
	TTCAGCTGCG AGCCTGACAG ACATGGGAGG CTCTGCGGC CGGGAGCTGG AGCGGGGGAG	420
	GAAACCCAAG TTGACAAGAA CTCAAAGTGC CTTTCTCCG GTCTCCTTCA GCCCCCTGTT	480
20	CACAGGTGAA ACTTGTCGCG TTGTGGATGT GGACATTTCT CAGCGGGGCC TGACCTCTCC	540
	ACACCCCTCA ACTCCCCCTC CTCTCCGAG AAGAGCCTC AGCCCTCTAG ATGATATCAG	600
25	TGGGACGCTG CCTACATCTG TCCCTGTGGC TCCGATGGGG TCTTCTCTGC AGTCTTTCCC	660
	CCTACCTCCG CCTCTCCAC CCCATGCCCC AGATGCATT TCCCCGGATTG CTCCCATCCG	720
30	AGCAGCTGAA TCCCTGACA GCCAACCCCC ACAGCACCTC CAGTGTCCCC TCTACCGGCC	780
	TGACTCGAGC AGCTTTGCAG CCAGCCTTCG AGAGTTGGAG AAGTGTGGTT GGTATTGGGG	840
	GCCAATGAAT TGGGAAGATG CAGAGATGAA GCTGAAAGGG AAACAGATG GTTCTTCCCT	900
35	GGTACGAGAC AGTTCTGATC CTCGTTACAT CCTGAGCCTC AGTTCCGAT CACAGGGTAT	960
	CACCCACCAC ACTAGAATGG AGCACTACAG AGGAACCTTC AGCCTGTGGT GTCATCCAA	1020
40	GTTTGAGGAC CGCTGTCAAT CTGTTGTAGA GTTTATTAAG AGAGCCATTA TGCACTCCAA	1080
	GAATGAAAG TTTCTCTATT TCTTAAGATC CAGGGTTCGA GGACTGCCAC CAACTCTGT	1140
	CCAGCTGCTC TATCCAGTGT CCCGATTCAG CAAATGTCAAA TCCCTCCAGC ACCTTGGAG	1200
45	ATTCCGGATA CGACAGCTCG TCAGGATAGA TCACATCCCA GATCTCCCA TGCTCAAACC	1260
	TCTGATCTCT TATATCCGAA AGTTCTACTA CTATGATCCT CAGGAAGAGG TATACCTGTC	1320
	TCTAAAGGAA GCGCAGCTCA TTTCAAACA GAAGCAAGAG GTGGAACCCCT CCACGTAGCG	1380
50	AGGGGCTCCC TGCTGGTCAC CACCAAGGGC ATTGGGTTGC CAAGCTCCAG CTGGAAAGAA	1440
	CCAAAATTAAG CTACCATGAA AAGAAGAGGA AAAGTGAGGG AACAGGAAGG TTGGGATTCT	1500
55	CTGTGCAGAG ACTTTGGTTC CCCACGCAGC CCTGGGGCTT GGAAGAAGCA CATGACCGTA	1560
	CTCTGGGTGG GGCTCCACCT CACACCCACC CCTGGGCATC TTAGGACTGG AGGGGCTCTT	1620
60	TGGAAAATG GAAGAAGTCT CAACACTGTGTT CTCTTCTCAA AAAAAAAA AAAAAAGATG	1680
	CGGGCGCAAG CTTATTCCTT TTAGTGGAGG TTAATTCTAG CTGGCACTG GCCGTGTTT	1740
	TACAACGTCG TGACTGGAA AACCCCTGGCG TTACCCAACT TAATCGCCTT GCAGCACATC	1800

CCCCTTTCGG CAGCTGGCGT	AATAGCGAAG AGGCCCGCAC CGATCGCCCT	TCCCAACAGT	1860
TCGGCAGCCT	GAATGGCGAA TGGGACGCGC CCTGTAGCGG CGCATTAACG CGCGCGGGT		1920
5	GTGGTGGTTA CGCGCAGCGT	GACCGCTACA CTTGCCAGCG CCCTACGCC GCTCCCTTCG	1980
	CTTCTTCCC TTCCCTTCTC	GCCACGTTCG CCGGCTTCC CCGTCAACTC TAATCGGGG	2040
10	GCTCCCTTA GGTTCCGATT TANTGCTTA CCCACTCNAC CCCAAAACCTT GATTAGGTGA		2100
	TGTCACTTAT GGACACNCCTG ATAACGTTTC CCCTTACTTT GATCACTTCT TTATATGATC		2160
	TTTCCAATGA AACATCACCT ACTCGTCATC TTTATTTAAA GATTG		2206
15	(2) INFORMATION FOR SEQ ID NO:29:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 1390 base pairs		
20	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(ii) MOLECULE TYPE: cDNA		
25			
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:		
30	CGGACGCGTG GGTTGGCTG TGAATATTCT ATTGCTGTG AGTATCTGTT TCTCTTCCTA		60
	GGCTCAAGTT GG TGACCCAA GCCTATTGTA AACAAAGTGAT TATCTCANN GGAGATGCCA		120
35	ATGGAGTAAC AATTGTTAA CCTTACGTTT TCTGTCTGTA TATTTTTTTA AAAATCTGGT		180
	AGTTTCTGGA AAAAAAGAG AAGGGGGTTT GTAGTACTTA ACCCTATTAA TTKSCRYRWG		240
	TTTTAGTTAA TTAGTTTTTG GAATAAAATGG ATTTCAGTAT AGCTTTGTGG TTAAATTGCA		300
40	TTGCTTTAT TTTATGTTTA GGCTTATTAA TAAATTAACA TTTAACAGAA ACATTGAAA		360
	TAGAATTTCG ATGTCTGCCT TAATTAACCTT AAAGACTGAT TTTAATCTGA CTATGACACT		420
45	GAGCATATTTC TTAAATTAC TCATAATTAA TAATGCTAA TATAATCTTA ATTAATTAA		480
	GCAGTTTTAG TATAAGATGT GCCATTGTTG CCTCTGTATG TCTGAATGAA GCTATAACAT		540
	TTGCCTTTTT ATTGCAGGTT TTCCCTTGGA ATATGGATAA ATACACCATG ATACGGAAAC		600
50	TAGAAGGACA TCACCATGAT GTGGTAGCTT GTGACTTTTC TCCGTGATGGA GCATPACTGG		660
	CTACTGCATC TTATGATACT CGAGTATATA TCTGGGATCC ACATAATGGA GACATTCTGA		720
55	TGGAATTCTGG GCACCTGTTT CCCCCACCTA CTCCAATATT TGCTGGAGGA GCAAATGACC		780
	GGTGGGTACG ATCTGTATCT TTAGGCCATG ATGGACTGCA TGTGCAAGTC CTTGCTGATG		840
	ATAAAATGGT GAGGTTCTGG AGAATTGATG AGGATTATCC AGTGCAAGTT GCACCTTGA		900
60	GCAATGGTCT TTGCTGTGCG TTCTCTACTG ATGGCAGTGT TTTAGCTGCT GGGACACATG		960
	ACGGAAGTGT GTATTTTGG GCCACTCCAC GGCAAGTCCC TAGCCCTGCAA CATTATGTC		1020
	GCATGTCAAT CGGAAGAGTG ATGCCACCC AAGAAGTCA GGAGCTGCCG ATTCCTTCCA		1080

AGCTTTGG A GTTCTCTCG TATCGTATTT AGAAGATTC GCCTCCCTA GTAGTAGGGA 1140
5 CTGACAGAAT ACACCTAACAA CAAACCTCAA GCTTACTGA CTTCAATTAT CTGTTTTAA 1200
AGACGTAGAA GATTTATTTA ATTTGATATG TCTCTGTACT GCATTTGAT CAGTTGARGC 1250
TTTTAAATA TTATTTATAG ACAATAGAAG TATTTCTGAA CATATCAAAT ATAAAATTTT 1320
10 TTAAAGATCT AACTGTGAAA AACATACATA CCTGTACATA TTTAGATATA AGCTGCTATA 1380
TGTTGAATGG 1390



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: C12N 15/12, C07K 14/47, 16/18, C12N 15/62		A3	(11) International Publication Number: WO 99/03993												
			(43) International Publication Date: 28 January 1999 (28.01.99)												
<p>(21) International Application Number: PCT/US98/14544</p> <p>(22) International Filing Date: 17 July 1998 (17.07.98)</p> <p>(30) Priority Data:</p> <table> <tr> <td>60/053,153</td> <td>18 July 1997 (18.07.97)</td> <td>US</td> </tr> <tr> <td>60/053,244</td> <td>18 July 1997 (18.07.97)</td> <td>US</td> </tr> <tr> <td>60/055,804</td> <td>15 August 1997 (15.08.97)</td> <td>US</td> </tr> <tr> <td>60/055,853</td> <td>15 August 1997 (15.08.97)</td> <td>US</td> </tr> </table> <p>(71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).</p> <p>(72) Inventor: JOHNSON, James, A.; 205 Mary Alice Drive, Los Gatos, CA 95032 (US).</p> <p>(74) Agents: MCLAUGHLIN, Jaye, P. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).</p>		60/053,153	18 July 1997 (18.07.97)	US	60/053,244	18 July 1997 (18.07.97)	US	60/055,804	15 August 1997 (15.08.97)	US	60/055,853	15 August 1997 (15.08.97)	US	<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 3 June 1999 (03.06.99)</p>	
60/053,153	18 July 1997 (18.07.97)	US													
60/053,244	18 July 1997 (18.07.97)	US													
60/055,804	15 August 1997 (15.08.97)	US													
60/055,853	15 August 1997 (15.08.97)	US													
<p>(54) Title: SUPPRESSORS OF CYTOKINE SIGNALING; RELATED REAGENTS</p> <p>(57) Abstract</p> <p>Purified genes encoding intracellular regulatory molecules from a human, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding these molecules are provided. Methods of using said reagents and diagnostic kits are also provided.</p>															

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 98/14544A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 C07K16/18 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. STARR ET AL: "A family of cytokine-inducible inhibitors of signalling" NATURE,, vol. 387, no. 6636, 26 June 1997, pages 917-921, XP002085491 LONDON GB cited in the application see the whole document ---	1-9
A	T.A ENDO ET AL: "A new protein containing an SH2 domain that inhibits JAK kinases" NATURE,, vol. 387, no. 6636, 26 June 1997, pages 921-924, XP002085492 LONDON GB cited in the application see the whole document ---	1-9
	-/-	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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Date of the actual completion of the international search

17 December 1998

Date of mailing of the international search report

15.04.99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 Rijswijk
Tel: (+31-70) 340-2000, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

LE CORNEC N.D.R.

INTERNATIONAL SEARCH REPORT

In' National Application No.
PCT/US 98/14544

C/(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	T. NAKA ET AL: "Structure and function of a new STAT-induced STAT inhibitor" NATURE., vol. 387, no. 6636, 26 June 1997, pages 924-929, XP002088455 LONDON GB cited in the application see the whole document ---	1-9
A	A. YOSHIMURA ET AL: "A novel cytokine-inducible gene CIS encodes an SH2-containing protein that binds to Tyrosine-phosphorylated interleukin-3 and erythropoietin" EMBO JOURNAL., vol. 14, no. 12, 1995, pages 2816-2826, XP002088456 EYNSHAM, OXFORD GB cited in the application see the whole document ---	1-9
P,X	WO 98 20023 A (THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH) 14 May 1998 see the whole document especially see examples 11,17,18 see page 101 - page 102 ---	1-9
P,X	M. MASUHARA ET AL: "Cloning and characterization of novel CIS family genes" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS., vol. 239, October 1997, pages 439-446, XP002088457 ORLANDO, FL US see the whole document ---	1-9
T	D.J. HILTON ET AL: "Twenty proteins containing a C-terminal SOCS box form five structural classes" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol. 95, January 1998, pages 114-119, XP002085497 WASHINGTON US see the whole document -----	1-9

INTERNATIONAL SEARCH REPORTinternational application No.
PCT/US 98/14544**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 5.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Please see extra sheet, Subject 1.

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: (1-9) all partially

Human SOCS14. Production by genetic engineering. Antibody.
Fusion protein.

2. Claims: (1-9) all partially

Murine SOCS15. Production by genetic engineering. Antibody.
Fusion protein.

3. Claims: (1-9) all partially

Murine SOCS17. Production by genetic engineering. Antibody.
Fusion protein.

4. Claims: (1-9) all partially

Human SOCS18. Production by genetic engineering. Antibody.
Fusion protein.

5. Claims: (1-9) all partially

human SOCS19. Production by genetic engineering. Antibody.
Fusion protein.

6. Claims: (1-9) all partially

Murine WDS12. Production by genetic engineering. Antibody.
Fusion protein.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/14544

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820023	A 14-05-1998	AU 4694397 A	29-05-1998